UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BOEHRINGER INGELHEIM INTERNATIONAL GMBH AND BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
PETITIONER

v.

BIOGEN, INC.
PATENT OWNER

CASE IPR2015-00418
Patent 8,329,172 B2

BIOGEN'S PATENT OWNER PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107

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TABLE OF ABBREVIATIONS

Abbreviation	Description
BCG	Bacilli Calmette-Guerin
CF	Chemotherapy combination of cyclophosphamide and fludarabine
CHOP	Chemotherapy combination of cyclophosphamide, vincristine, doxorubicin, and prednisone
CR	Complete response (also complete remission)
CVP (aka COP)	Chemotherapy combination of cyclophosphamide, vincristine, and prednisone
DLBCL	Diffuse large B-cell lymphoma
HG-NHL	High-grade NHL
IFN	Interferon
IG-NHL	Intermediate-grade NHL
LG-NHL	Low-grade NHL
MoAb	Monoclonal antibody
MRD	Minimal residual disease
NHL	Non-Hodgkin's lymphomas
OS	Overall survival
ORR	Overall response rate
PR	Partial response (also partial remission)
PFS	Progression-free survival
RTX	Rituximab
TTP	Time to progression

I. INTRODUCTION

Low-grade non-Hodgkin's lymphoma (LG-NHL) is a deadly cancer that is "low grade" in name only. It is incurable—those suffering are plagued by repeated relapses even after responding to chemotherapy. Before the invention, attempts to prevent relapse with maintenance therapy failed, and no maintenance regimen provided a definitive improvement in survival.

Then came a new treatment regimen—CVP induction with rituximab maintenance, as claimed in U.S. Patent No. 8,329,172 (the "'172 patent") to Biogen, Inc. (formerly "Biogen Idec" and "Idec").[1] This treatment prolonged progression-free survival in LG-NHL to a far greater extent than any prior strategy, and with minimal toxicity.

Petitioners Boehringer Ingelheim International, GmbH and Boehringer Ingelheim Pharmaceuticals, Inc. (together "Boehringer") request *inter partes* review of the sole claim of the '172 patent, which is narrowly tailored to treating LG-NHL with CVP induction followed by rituximab maintenance therapy given as four weekly doses of 375 mg/m^2 every six months for two years. The Board should deny Boehringer's request.

Boehringer's principal patentability challenge relies on copies of cover memos and study protocols for two Phase III clinical trials jointly run by Biogen and Eastern

[1] "CVP" is chemotherapy with **C**yclophosphamide, **V**incristine and **P**rednisone.

Cooperative Oncology Group (ECOG) to study rituximab maintenance therapy in LG-NHL and intermediate-grade NHL (IG-NHL). Fatal to Boehringer's proposed grounds, however, is the lack of evidence showing that these protocols (ECOG 1496 and 4494) are actually prior art "printed publications."

Boehringer asserts that a person of ordinary skill would have been able to find these rituximab study protocols—which it does not claim were published in any journal or available in any library—by "simply searching" the ECOG website. But the proffered evidence shows the opposite: ECOG's 1998 website was not searchable, the word "rituximab" is nowhere to be found on it, and the page Boehringer cites as purportedly disclosing the protocols did not in fact contain the protocols themselves—or even links to them—but instead only obscure protocol titles. Boehringer utterly fails to show the indexing or cataloguing the law requires to establish that such documents were "printed publications." In fact, pages of the 1998 ECOG website omitted by Boehringer suggest that distribution of protocols was restricted; these omitted pages show that the members section of the ECOG website was password-protected. Boehringer also fails to show that an interested member of the public who somehow found out about the protocols could actually have obtained copies of what are now Exhibits 1003 and 1004 before the critical date of the '172 patent. Boehringer, simply put, provides no competent evidence of whether, when, and to what extent, copies of the protocols were actually distributed or accessible, within or outside of ECOG, prior to the priority date.

Instead of identifying and establishing facts proving whether the protocols were publicly accessible—and if so, when—Boehringer relies on speculation by its proposed expert, Dr. Michael Grossbard, as to how cooperative research groups similar to ECOG "typically" might have operated. Dr. Grossbard was not then, and is not now, a member of ECOG. His testimony is conjecture, and the Federal Circuit has held such conjecture to be insufficient to establish dissemination under the printed-publication analysis. Indeed, it is telling that despite bearing the burden of establishing that the protocols were "printed-publication," Boehringer never says how or when (in the sixteen years since the patent was filed) it obtained copies of the protocols. If these protocols had been widely distributed, as Boehringer suggests, then surely Boehringer would have found people who had actually received them before the priority date or, at the very least, a witness personally familiar with ECOG's operations. Instead, it relies on Dr. Grossbard's speculation about what an organization in which he has never been a member, or otherwise played a role, might "typically" have done. Dr. Grossbard's speculation simply cannot satisfy Boehringer's burden of proving that the ECOG protocols were prior art printed publications.

As for Boehringer's other cited references, none teaches ***any*** of the material limitations of the claim: (1) rituximab maintenance therapy in LG-NHL, (2) rituximab maintenance therapy following CVP induction, and (3) the rituximab maintenance regimen of four weekly doses of 375 mg/m^2 every six months for two years. In its attempt to fill in these gaps, Boehringer simply pieces together disparate portions of

different references for each claim element, providing little reasoning on why a skilled artisan would have combined such references, or why there allegedly would be a reasonable expectation of success in practicing the claimed method. Boehringer ignores, for example, that LG-NHL responded differently to chemotherapy than IG-NHL; that the combination of CHOP chemotherapy[2] with rituximab was highly effective in LG-NHL and thus there would not have been a reason to switch to CVP; and that rituximab treatment in the maintenance setting would warrant lower doses than that used in relapsed-disease because of the difference in tumor burden. Boehringer also implausibly asserts that clinical experience with interferon would translate to rituximab, even though the two drugs have entirely different mechanisms of action, simply because both are "biologics." Boehringer's petition does not establish even a *prima facie* showing of obviousness, much less the likelihood of success required to initiate trial.

Boehringer also fails to rebut evidence in the examination record of objective indicia of non-obviousness. Boehringer's grievance with the evidence of unexpected results—and relatedly, the proclaimed "foundation" of its petition—is that "publications disclosing maintenance therapy for the treatment of LG-NHL were not cited during prosecution" and not considered by the Office when it accepted evidence

[2] "CHOP" is chemotherapy regimen with **C**ytoxan® (cyclophosphamide), **H**ydroxydaunorubicin (a.k.a. doxorubicin), **O**ncovin® (vincristine) and **P**rednisone.

of unexpected results. Boehringer's characterization of the examination record is demonstrably false. The Office reviewed, for example, publications disclosing interferon maintenance therapy in LG-NHL. Boehringer's attack on findings of unexpected results and non-obviousness does not withstand scrutiny.

II. BACKGROUND

A. Technical Overview of the Invention

1. Various Non-Hodgkin's Lymphomas

Although sometimes referred to in the singular form, NHL "is not a single disease but a diverse group of diseases ranging from the very aggressive and rapidly fatal to the more indolent." Ex. 1024 at 1382. "Low-grade lymphoma usually presents as a nodal disease, and is often indolent or slow-growing," whereas "intermediate and high-grade disease usually presents as a much more aggressive disease." Ex. 1001 at 4:49-52. The type of lymphoma is the "the major determinant[] for treatment outcome and prognosis" because the diseases differ "in sensitivity to [] chemotherapy." Ex. 1011 at 2141-42. For this reason, the term "low-grade" is something of a misnomer from the patient's perspective. At the time of the invention, a diagnosis of LG-NHL meant a very poor prognosis. The disease was (and still is) a "chronic, incurable cancer." Pet. 15. Patients with LG-NHL had constant cancer relapses even after responding to chemotherapy. In contrast, patients with intermediate- and high-grade NHL were frequently curable. *See* Ex. 1011 at 2142.

2. Treatment of LG-NHL and IG-NHL

Traditionally, the type of lymphoma a patient suffered from dictated the chemotherapeutic regimen used. Most chemotherapy regimens that were used for LG-NHL were not used for IG-NHL, and vice versa. *Compare* Ex. 2001 at 1082, Table 111-7 (listing chemotherapy used for LG-NHL) *with id.* at 1084, Table 111-8 (listing chemotherapy used for intermediate- and high-grade lymphomas). CHOP chemotherapy was an exception, as it was used for both. *Id.*; *see also infra* Section V.A.2. The goal of such chemotherapy (often referred to as "induction" or "first-line" therapy) was to induce the cancer into remission.

At the time of the invention, there was a significant unmet medical need for effective maintenance therapy to maintain remission and prevent relapse of LG-NHL. Standard chemotherapeutic agents that were successful as first-line therapies were unfortunately not successful as maintenance. Pet. 19. This was because of, for example, "increased toxicity, reduced patient well-being, and increased risk of secondary malignancies." Ex. 1042 at 3295.

Dr. Grossbard and Boehringer suggest that prior-art biologics such as BCG (traditionally a tuberculosis vaccine) and interferon (a cytokine also used to treat infections) were successful as maintenance therapy. *See* Ex. 1002 ¶ 66. This is incorrect—BCG had long been abandoned as maintenance therapy for LG-NHL by the time of the invention. As one textbook explained:

> [T]he considerable number of clinical trials undertaken with . . . BCG [and other immunomodulators] have failed to demonstrate positive effects of these agents on complete remission rates or remission durations . . . . BCG immunotherapy [has] failed to improve disease-free survival in this [LG-NHL] disease setting. Thus, the weight of evidence does not provide a compelling reason to recommend further study . . . as maintenance therapy.

Ex. 2002 at 699-700. Interferon was likewise unsuccessful as maintenance therapy. *See infra* Section V.C.2. Due to failed efforts to develop successful maintenance therapy for LG-NHL, "[m]aintenance therapy [was] ***rarely employed*** in non-Hodgkin's lymphoma once a clinical complete response has been obtained." Ex. 2003 at 912 (emphasis added).

3. Rituximab

Rituximab, the first monoclonal antibody approved to treat cancer, binds to the CD20 antigen on B-cells, facilitating their destruction. *See* Ex. 1001 at 1:47-50, 5:35-43. Most B-cell lymphomas express CD20. *Id.* at 1:27-41. A known danger of multiple treatments with rituximab was antigen escape, whereby the lymphoma would develop resistance to rituximab by losing expression of CD20. *See* Section V.A.1.b. below.

In November 1997, the FDA approved rituximab as monotherapy to treat relapsed or refractory, low-grade or follicular NHL. Ex. 1008 at 1. Even before this approval, Biogen (then IDEC Pharmaceuticals) began working with other investigators, notably with ECOG, to test rituximab in other lymphoma settings, including as first-line and maintenance therapy in IG-NHL. Based on these studies, in

February 2006, the FDA approved rituximab as first-line therapy in combination with CHOP for one histological type of IG-NHL (DLBCL), but did ***not*** approve rituximab as maintenance therapy in DLBCL because it failed to show efficacy. *See* Ex. 1041 at abstract; Ex. 2004 at 17-18. It was not until September 2006 that the FDA approved rituximab as maintenance therapy following CVP induction in LG-NHL, as claimed in the '172 patent. *See* Ex. 2010 at 16.

B. Prosecution History

The '172 patent traces its lineage back to a provisional application (60/096,180) filed on August 11, 1998. Boehringer argues that claim 1 cannot claim priority to this provisional application. For simplicity in this Preliminary Response only, Biogen will assume that the priority date is the non-provisional filing date of August 11, 1999, without waiving its right to argue otherwise later.

During examination, the Patent Office issued a restriction requirement compelling Biogen "to elect a particular form of NHL" because the different types of NHL are patentably distinct. *See* Ex. 2005 at 2. The Office also compelled Biogen to elect "a specific chemotherapy protocol" because the different chemotherapy regimens are patentably distinct. *Id.* Biogen elected LG-NHL and CVP therapy. Ex. 2006 at 8. Boehringer's present attempt to challenge patentability by equating IG-NHL with LG-NHL, and CHOP therapy with CVP therapy, contradicts the Office's view that these cancers and treatments are significantly different.

In its petition, Boehringer relies upon many references that are cumulative to those Biogen overcame during examination. *Compare* Exs. 1007-1009 *with* references addressed in Ex. 1064 at 4-6 (Press Release, Bierman, and Grillo-Lopez). During examination, Biogen also established objective indicia of non-obviousness, as discussed in Section VI below.

Boehringer contends that "publications disclosing maintenance therapy for the treatment of LG-NHL were not cited during prosecution." Pet. 4. This is demonstrably false. The Office considered, for example, at least three clinical publications evaluating interferon maintenance therapy in LG-NHL, including Exs. 1067 and 1034 from Boehringer's petition. *See* Ex. 2007 at 7, 15, 25 (references D100, D200, and D338).

III. CLAIM CONSTRUCTION

Boehringer's proposed constructions should be rejected because they are inconsistent with the '172 patent disclosure and its prosecution history, and ordinary meaning. *See Tempo Lighting, Inc. v. Tivoli, LLC*, 742 F.3d 973, 977 (Fed. Cir. 2014) (identifying all three types of evidence as important in construing patent claims at the PTO under the broadest reasonable interpretation).

A. "A method of treating low grade B-cell non-Hodgkin's lymphoma in a human patient comprising"

Instead of proposing a construction as required by 37 C.F.R. § 42.104(b)(3), Boehringer cryptically suggests that the word "comprising" means that claim 1

"encompasses, among other things, additional forms of treatment that may be administered to the patient as long as the patient is administered 'chemotherapy consisting of CVP therapy . . . .'" Pet. 12. Because the petition does not rely on this comment, the Board need not construe this phrase. In any event, if Boehringer's position is that the initial "comprising" transition overrides the "chemotherapy ***consisting of*** CVP therapy" limitation, Boehringer is wrong. *See Georgia-Pacific Corp. v. United States Gypsum Co.*, 195 F.3d 1322, 1326-28 (Fed. Cir. 1999) (in claim reading "[a] gypsum board ***comprising*** a set [of mats], each of said mats ***consisting*** of randomly distributed glass fibers," "mats that 'consist' of glass fibers are made up of glass fibers and nothing else" (emphasis added)). Thus, the claim encompasses only CVP induction chemotherapy, as opposed to, e.g., CHOP, which adds doxorubicin.

B. "administering to the patient chemotherapy consisting of CVP therapy to which the patient responds"

Biogen agrees with some, but not all, of Boehringer's proposed construction for the term "to which the patient responds." Biogen disagrees with the portion of Boehringer's construction shown struck through here: "patient who responds to 'chemotherapy consisting of CVP' will have ~~a response, including, for example,~~ a complete response (CR) or a partial response (PR)." Pet. 12. The strikethrough removes Boehringer's contention that the patient's response can take any form. That is inappropriate because the patent defines a patient who "responds" as someone who experiences a CR or a PR. *See* Ex. 1001 at 9:21-22 ("Patients who did not achieve a

CR or PR were considered non-responders."); *see also id.* at 10:18-21 (describing overall responsiveness as only CR and PR); 13:31-34 (same).

Boehringer also presents constructions for the terms "complete response" and "partial response" even though neither term appears in the claims. Boehringer argues that "[w]hen a patient has a complete response or complete remission (CR), the patient will have only minimal residual disease (MRD)," and "[w]hen a patient has a partial response or partial remission (PR), the patient will have a substantially reduced tumor burden." Pet. 12. There is no need to define further these terms. *See Sonix Tech. Co. v. Publications Int'l, Ltd.*, No. 13-CV-2082, 2014 WL 5489353, at *9 (N.D. Ill. Oct. 30, 2014) (finding "a derivative construction . . . not necessary to elucidate the claim's meaning"). But if this Board does construe these terms, it should not adopt Boehringer's proposed definitions, which are inconsistent with intrinsic and extrinsic evidence.

The '172 patent disclosure expressly defines the criteria for complete and partial responses:

> ***Complete response*** required the regression of all lymph nodes to <1×1 cm^2 demonstrated on two occasions at least 28 days apart on neck, chest abdomen, and pelvic CT scans, resolution of all symptoms and signs of lymphoma, and normalization of bone marrow, liver, and spleen. ***Partial response*** required a ≧50% decrease in the sum of the products of perpendicular measurements of lesions without any evidence of progressive disease for at least 28 days.

Ex. 1001 at 9:14-21 (emphasis added). Boehringer's proposed definitions of CR and PR fail to comport with these definitions. If the Board considers it necessary to construe CR and PR, it should adopt the specification's express definitions. *See Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1380 (Fed. Cir. 2009) ("When a patentee explicitly defines a claim term in the patent specification, the patentee's definition controls.").

Boehringer's proposed definitions of CR and PR also are inconsistent with ordinary meaning. Boehringer's own references, for example, expressly distinguish CR and MRD. *See, e.g.*, Ex. 1033 at 153-54 ("IFN may preferentially be used in patients with minimal residual disease ***or*** in patients in CR following conventional chemotherapy."); Ex. 1040 at 1608 (setting different criteria for CR and minimal residual disease). Boehringer's attempt to equate PR with a vaguely defined notion of "substantially reduced tumor burden" is similarly inconsistent with its own cited reference. *See* Ex. 1040 at 1608 (defining PR quantitatively as "≧50% reduction in the sum of the products of the diameters of measurable lesion"). It is not surprising that the only evidence Boehringer advances is unsupported expert testimony. *See* Pet. 12-13; Ex. 1002 ¶¶ 29, 57.

C. "followed by rituximab maintenance therapy"

This phrase implicates two constructions—one for "maintenance therapy" and another for "followed by." Biogen agrees with most, but not all, of Boehringer's proposed construction for "maintenance therapy." Specifically, Biogen agrees with the

parts of Boehringer's construction ***not*** shown struck through here: "administering rituximab after 'chemotherapy consisting of CVP' for the purpose of ~~treating the patient's MRD (for patients who responded with CR),~~ prolonging remission and~~/or~~ to prevent relapse." *See* Pet. 14. Biogen disagrees with Boehringer's attempt to add the concepts of treating a patient's MRD, and Boehringer's suggestion that maintenance therapy envisions prolonging remission or preventing relapse as alternative outcomes. Neither point comports with the ordinary meaning of "maintenance therapy." The ordinary understanding of maintenance therapy is therapy that prolongs remission and prevents relapse. *See* Ex. 2002 at 722 ("An alternative philosophy has been to induce remission and then to administer maintenance therapy of one type or another, to try ***to prevent recurrence***.").

Boehringer's proposed construction wrongly incorporates the concept of MRD into the claim term "maintenance therapy." Dr. Grossbard fails to cite any authority for his proposed definition of "maintenance therapy" as encompassing treatment of MRD. *See* Ex. 1002 ¶¶ 32, 42, 113-14. This lack of evidence is not surprising because a person of ordinary skill would have understood that treating minimal residual disease is not maintenance therapy. Dr. Grossbard in his own publications has used the terms "minimal disease" and "maintenance therapy" as describing different treatment settings:

> [Monoclonal antibodies] 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 at 3704 (emphasis added).

Boehringer proposes that the phrase "followed by" be construed as "that the 'rituximab maintenance therapy' is administered at any time after the patient has responded to the chemotherapy consisting of CVP therapy." Pet. 13. Boehringer does not rely on this proposed construction, and the Board therefore is not required to construe this phrase.

If the Board chooses to construe "followed by," it should not adopt Boehringer's proposed construction, which is plainly incorrect insofar as it is read to encompass administering rituximab to treat relapsed disease. As Boehringer acknowledges, "maintenance therapy" is therapy used for "prolonging remission" and "to prevent relapse." Using rituximab to treat relapsed disease is not prolonging a remission (because remission has already ended) or preventing a relapse (because relapse has already occurred). Indeed, during examination, Biogen repeatedly distinguished rituximab maintenance therapy from cited art disclosing rituximab as a treatment for relapsed disease. *See, e.g.*, Ex. 2009 at 30 ("Each reference refers to treatment of ***relapsed patients, rather than responsive patients***, and provided no incentive to select responsive patients, much less those who responded to CVP

therapy specifically, for ***maintenance therapy*** with rituximab." (emphasis added)); Ex. 1064 at 5.

Thus, if the Board determines it necessary to construe "followed by" (and there is no need to do so), it should construe it as "that the 'rituximab maintenance therapy' is administered at any time after the patient has responded to the chemotherapy consisting of CVP therapy and before disease relapse" (addition to Boehringer's proposed construction underlined). This is the only construction faithful to the phrase "maintenance therapy" in the claims, the specification and examination record.

D. "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"

Boehringer suggests that the "comprising" language means the "period of time" for rituximab maintenance therapy can be continued for longer than two years. Pet. 15. As Boehringer's petition does not rely on this comment in its proposed grounds, the Board need not construe this clause.

IV. BOEHRINGER FALLS FAR SHORT OF ESTABLISHING THAT THE ECOG PROTOCOLS ARE PRINTED PUBLICATIONS

A patent claim can be challenged in *inter partes* review "only on the basis of prior art consisting of patents or printed publications." 35 U.S.C. § 311(b); *see also Cisco Sys., Inc. v. Constellation Techs. LLC*, IPR2014-01085, Paper 11 at *5 (P.T.A.B. Jan. 9, 2015) ("Petitioner has not made a sufficient showing that Rosenberg qualifies as a printed publication under 35 U.S.C. § 102(b) and, thus, falls within the proper scope

of an *inter partes* review."). Boehringer's petition principally relies on two clinical trial protocols from ECOG and Biogen[3]—Exhibits 1003 and 1004—that are not "printed publications" because Boehringer has not shown that they were publicly accessible before the priority date of the '172 patent. Because Boehringer has not met its burden in this regard, trial cannot be instituted based on either reference.[4]

A. A Reference Must Have Been "Publicly Accessible" To Be A Printed Publication.

"'[P]ublic accessibility' has been called the touchstone in determining whether a reference constitutes a 'printed publication' bar under 35 U.S.C. § 102(b)." *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008). "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

[3] These studies were part of a collaboration of "NCI Division of Cancer Treatment and Diagnosis . . . with IDEC Pharmaceuticals Corporation to explore Rituximab treatment in other indications." *See* Ex. 2012 at 246-47.

[4] At this time, and without waiving any objections, Biogen is not asking the Board to exclude Boehringer's evidence regarding the ECOG protocols on evidentiary grounds. *Cf.* 37 C.F.R. § 42.64. Even if all of Boehringer's evidence regarding the ECOG protocols were admissible, that evidence could not support a conclusion that the protocols qualify as printed publications.

locate it." *Id.* This raises at least two questions. First, could a person of skill have located the reference? *See id.* at 1196 ("The record . . . does not show that an anonymous user skilled in the art in 1997 would have gained access to the FTP server and would have freely navigated through the directory structure to find the Live Traffic paper."). Second, once the reference was located, would a person of skill have been given access to the reference? *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 936-37 (Fed. Cir. 1990) (disclosure within a limited group of persons and organizations does not make a document "generally available"). Measured under these standards, neither Ex. 1003 nor Ex. 1004 is a printed publication.

B. The ECOG Protocols (Exhibits 1003 and 1004) Are Not Section 102(b) Printed Publications Because There Is No Evidence That The Protocols Were Publicly Accessible.

Boehringer argues that the ECOG protocols are "printed publications" based on assertions that: (1) a skilled artisan allegedly could have, by May 1998, learned about the ECOG 1496 and ECOG 4494 clinical trials by searching the ECOG website for clinical trials pertaining to rituximab; (2) the protocols for these trials were allegedly available, by May 1998, to any interested physician who requested them; and as a result (3) the ECOG protocols were "publicly available and disseminated." Pet. 29-30, 1-2. None of these assertions is supported by competent evidence.

1. There Is No Evidence That A Person Of Skill Exercising Reasonable Diligence Would Have Located The Protocols.

Boehringer's argument for publication of the ECOG protocols is predicated on the notion that "[a] copy of the ECOG website from May 19, 1998, announced to the public that protocols for both trials were 'active' as of May 1998. Ex. 1022." Pet. 28. Boehringer says nothing about how the website "announced" the protocols "to the public" except to assert that a person of skill could have "simply search[ed] the ECOG website for clinical trials pertaining to rituximab." Pet. 29.

But the ECOG website ***did not have a search function*** in 1998. Boehringer relies on the Internet Archive or "Wayback Machine" (www.archive.org) for its evidence concerning the 1998 ECOG website. But using that same tool reveals that as of May 1998 the ECOG site had no operative search function. *See* Ex. 2011 at 107 (Clicking the "Search" link on the left-hand box of links in the archived page results in the message: "Search ECOG Site—Sorry, this function is not yet available."). Boehringer neglects to provide the Board with this critical page from the archived ECOG website. The page undermines Boehringer's assertion that one could have "simply search[ed]" the ECOG website during the relevant time period.

Moreover, even if there had been a search function, it would have done no good because neither "Rituxan" nor "rituximab" appeared anywhere on the ECOG website as captured by the Internet Archive. Boehringer submits only a single page from the ECOG website, Ex. 1022. A complete version of the archived website is

provided with this Response as Ex. 2011. A review of each page of the complete archived website shows that "simply searching the ECOG website for clinical trials pertaining to rituximab," Pet. 29, would have yielded absolutely nothing.

Other than its unsupported and inaccurate "simpl[e] search" argument, Boehringer provides no explanation of how or why a person of skill in the art allegedly would have found the specific webpage in question (Exhibit 1022). This is fatal to Boehringer's printed publication argument for at least two reasons. First, even if Exhibit 1022 actually disclosed substantive aspects of the claimed invention (which even Boehringer does not contend), the "printed publication" requirement is not satisfied where, as here, the webpage was at most only available to persons of skill who happened to know of its existence. *See Groupon, Inc. v. Blue Calypso LLC*, CBM2013-00044, Paper 47 at 20 (P.T.A.B. Dec. 17, 2014) (finding that a paper was not a printed publication where it "was only available for viewing and downloading to members of the public who happened to know that the [] paper was there"); *see also SRI Int'l,* 511 F.3d at 1196 ("The record . . . does not show that an anonymous user skilled in the art in 1997 would have gained access to the FTP server and would have freely navigated through the directory structure to find the Live Traffic paper."); *Samsung Elecs. Co. v. Rembrandt Wireless Tech.*, IPR2014-00514, Paper 18 at 8 (Sept. 9, 2014) ("Petitioner has not presented persuasive argument or evidence regarding how members of the potentially interested public would have been made aware of these meetings").

Second, Exhibit 1022 does not contain or provide access to the protocols themselves and does not describe them with detail sufficient to indicate that they are likely to contain relevant information. To the extent Boehringer is suggesting Exhibit 1022 makes the protocols printed publications by serving as an appropriate index, it is wrong as a matter of law. To constitute a printed publication, a document must be catalogued or indexed in "a meaningful way." *In re Cronyn*, 890 F.2d 1158, 1161 (Fed. Cir. 1989). Here, Exhibit 1022 itself (the alleged index) is not catalogued or searchable in any way, making it of no value as a search aid. Moreover, even if a person of skill had happened upon Exhibit 1022, it would not lead such a person to seek a copy of the underlying protocols. ECOG 1496, for example, is described in Exhibit 1022 only as "A Randomized Phase III Study in Low Grade Lymphoma Comparing Cyclophosphamide/ Fludarabine to Standard Therapy Followed by Maintenance Biologic Therapy." Nothing in this title suggests that the protocol relates to rituximab. The reference to "biologic therapy" does not indicate to the skilled person any relation to rituximab in particular. *See* Exhibit 1013 (broadly describing "biologic therapy" as "immunotherapy (such as vaccines, cytokines, and some antibodies), gene therapy, and some targeted therapies").

In sum, Boehringer's theory that a person of skill would have searched an unsearchable website, and then sought and obtained copies of the ECOG protocols on the basis of that website, does not satisfy Boehringer's burden to prove that the protocols were "printed publications."

2. There Is No Evidence That The Protocols Were Accessible To The Public.

Even if a reference could be located by particular individuals, it is not a printed publication unless it is "generally available" to the public. *Northern Telecom*, 908 F.2d at 936-37. For example, in *Northern Telecom*, documents that were not under security classification and had been distributed to approximately fifty collaborating organizations and persons were nevertheless found not to be printed publications because of insufficient evidence "that ***anyone*** could have had access to the documents by the exercise of reasonable diligence." *Id.* at 936-37 (emphasis added); *see also Actavis, Inc. v. Research Corp. Techs., Inc.*, IPR2014-01126, Paper 22 at 10-12 (Jan. 9, 2015) ("Petitioner asserts that the LeGall thesis is available through University of Houston's library but provides no competent evidence to show that the library allows public access to the thesis."); *Samsung*, IPR2014-00514, Paper 18, at 6 ("[N]otwithstanding Mr. O'Hara's statement that passwords were distributed to the 802.11 Working Group e-mail list, the fact that an interested individual needed to contact IEEE in order to obtain a password or other means of accessing Draft Standard (and needed to know who to contact in the first place) weighs against public accessibility").[5]

[5] Boehringer refers to the dates that the ECOG 4494 and 1496 trials were "activated," but does not argue that the activation (or "start date") of a trial creates a printed publication by itself. This is appropriate, for the date the study started has no bearing

Boehringer offers no evidence (aside from Dr. Grossbard's speculation, addressed in Section IV.B.3. below) that the ECOG protocols were publicly accessible (or indeed even accessible to all ECOG member organizations), before the filing date. Boehringer's assumption that Exhibits 1003 and 1004 must have been publicly available because they are labeled "active" is not only unsupported, it is contrary to the evidence. For example, the NCI guidelines provide for confidentiality of protocols in NCI-funded investigations involving cooperatives such as ECOG, even after such studies are underway. *See* Ex. 2013 at 1 ("The Cooperative Group shall either be required to maintain the confidentiality of the material or, at its option, decline acceptance to any confidential materials. ***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." (emphasis added)).

Boehringer offers no evidence that the ECOG protocols were free from confidentiality restrictions before the priority date. *See id.* ("The duration of the confidentiality generally shall be a minimum of three years . . . ."). Instead, the evidence Boehringer points to again undercuts its own assertions. On the archived

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on whether there was a printed publication for purposes of § 102(b) analysis. *See Northern Telecom*, 908 F.2d at 936-37 (disclosure within a limited group of persons and organizations does not make a document "generally available").

ECOG website that Boehringer cites, the link to the members-only section was password-protected, not freely available publicly. Ex. 2011 at 2 (link at left reads "ECOG MEMBERS INFORMATION (password required)"). *See Samsung*, IPR2014-00514, Paper 18, at 6 ("the fact that an interested individual needed to contact IEEE in order to obtain a password or other means of accessing Draft Standard (and needed to know who to contact in the first place) weighs against public accessibility"). Boehringer's lack of evidence about who would have a password or how someone could get a password further illustrates the insufficiencies of Boehringer's proof.[6]

Boehringer's contention that the ECOG protocols were publicly available is also inconsistent with the fact that the protocol titles in Exhibit 1022 are not hyperlinks. This can be seen from the blue text and underlining absent from the titles but present in the "Back" and "How to contact ECOG" links at the bottom of Exhibit 1022; this also can be verified on the archived website at: https://web.archive.org/web/19980519084342/http:/ecog.dfci.harvard.edu/~ecogdba/active_reports/Lymphoma.html. Thus, an Internet user (whether an ECOG member or a member of the general public) could not have retrieved copies of the protocols via the webpage reproduced in Exhibit 1022. Boehringer presents no

[6] Although it includes as an exhibit a list of ECOG member organizations, Boehringer does not even purport to offer evidence identifying any individual in any of those organizations who actually had password access to the ECOG website.

other evidence that a member of the public could have obtained in an unrestricted manner a copy of the ECOG protocols from the ECOG website prior to the critical date—and not even Dr. Grossbard suggests as much. Because the members' area of the ECOG website was password-protected, the Internet Archive evidence presented by Boehringer cannot demonstrate, and Boehringer certainly has not presented any other evidence showing, that copies of the protocols were publicly accessible via the ECOG website prior to the critical date.

Boehringer next argues that persons of skill alternatively could have obtained the protocols from the NIH's PDQ database. Pet. 29. Here again, Boehringer resorts to speculation in lieu of proof. Boehringer cites Exhibit 1053 as support for its assertion that physicians could have obtained from PDQ "the protocol schema used in the ECOG trial." But Exhibit 1053 is merely a copy of the "Table of Contents" of the NCI's PDQ Cancer Database from January 1998; it makes no specific reference to ECOG-1496, ECOG-4494, or any other particular protocol or study. It is not a copy of either study protocol, nor even a description of either study, and it provides no evidence suggesting these particular protocols were available to the public via PDQ. Exhibit 1053 also makes clear on its face that PDQ at best contains only "summaries of trials" (presumably what Boehringer means by "schema"). But Boehringer offers no evidence whatsoever that summaries of ECOG 1496 or 4494 were available on PDQ before the critical date, much less evidence that the (imagined) content of those summaries would somehow establish that the protocols themselves were printed

publications.

Boehringer once again overlooks (or ignores) the content of its own evidence. It offers Exhibit 1049, a page from the ClinicalTrials.gov database, as support for its contentions, but disregards the notation, at the very top of that page, that ECOG 1496 was "***First received: May 2, 2000***," well after the August 11, 1999 filing date of the '172 patent. Moreover, the current entry in the PDQ database for ECOG 1496 states that PDQ's "[i]nformation about this trial [ECOG 1496] is from the ClinicalTrials.gov database." Ex. 2016 at 4. Thus, the only evidence of record, as established by Boehringer's own Exhibit 1049, is that the ECOG protocol was not available on PDQ/Clinicaltrials.gov until nearly ***nine months after*** the '172 patent filing date. Boehringer's assertions to the contrary simply constitute speculation and fail to meet its burden of showing that the ECOG protocols are printed publications.[7]

[7] Ex. 1052 is another post-invention reference cited by Boehringer. It is undated, and Boehringer's expert inconsistently characterizes it as being published in August 1999 and August 1997. *Compare* Ex. 1002 ¶ 102 *with id.* fn. 84. To clarify the record, the reference post-dates the '172 filing date, as evidenced by the stamped received date of September 2, 1999 on a copy obtained from a local library. Ex. 2012 at 2, 3. It is the "date of receipt" that determines the publication date. *See Carella v. Starlight Archery & Pro Line Co.*, 804 F.2d 135, 139 (Fed. Cir. 1986). The reference is therefore irrelevant to whether the ECOG protocols were publicly available before the filing date.

3. Dr. Grossbard's Testimony Does Not Establish Public Accessibility.

Given the lack of any documentary evidence that the ECOG protocols were distributed and accessible even among ECOG members, much less to the public, before the priority date, Boehringer tries to shore up its position by offering the testimony of Dr. Grossbard. *See* Pet. 28-30. But Dr. Grossbard, who apparently has never been a member of ECOG, has no firsthand knowledge of how the two ECOG protocols were handled, and does not even claim to have knowledge about ECOG's particular practices.

Even if Dr. Grossbard somehow were deemed to have general knowledge about ECOG practices based on his experiences with an entirely different organization, such knowledge would be insufficient. Testimony regarding "general practices" regarding availability upon request is insufficient to establish dissemination sufficient to qualify as a printed publication. In *Norian Corp. v. Stryker Corp.*, for example, the Federal Circuit agreed that a purported prior-art reference "did not meet the criteria of § 102(b) because it was available only upon individual request to the authors, and that ***such request and dissemination had not been shown***." 363 F.3d 1321, 1330 (Fed. Cir. 2004) (emphasis added). The Federal Circuit reasoned that "[a]lthough there was ***testimony that it was the general practice*** at IADR meetings for presenters to hand out abstracts to interested attendees, the lack of substantial

evidence of actual availability of the Abstract adequately supports the court's conclusion that dissemination of the Abstract was not established." *Id.*

The *Norian* rule is part of a larger body of case law requiring specific firsthand knowledge to establish that a publication is prior art. For example, in *AT&T Corp. v. Microsoft Corp.*, No. 01-4872C (WHP), 2004 WL 292321, at *6 (S.D.N.Y. Feb. 17, 2004), the Court found no evidence of printed publication despite testimony from an expert that, based on his experiences attending ICAASP conferences, papers presented at such a conference would have been distributed during the conference. *Id.* at *6. The court reasoned that the expert's "declaration rests on 'assumptions,' not facts since he neither attended the ICAASP Conference, nor received a copy of the 1980 Paper." *Id.*

Dr. Grossbard similarly lacks firsthand knowledge regarding distribution of the ECOG protocols. Dr. Grossbard has never even been a part of ECOG. He has only been involved with what he calls "similar cooperative groups." Ex. 1002 ¶ 99. Accordingly, his declaration asserts only that "clinical trial protocols are ***typically*** not provided to members of the cooperative under any confidentiality restrictions" and that there is a "***general*** absence of any confidentiality restrictions imposed on the protocols." *Id.* (emphasis added). This vague testimony regarding the perceived "general practice" of other groups fails the requirements set forth in *Norian* and other cases regarding firsthand knowledge and proof of actual availability.

Tellingly, Dr. Grossbard's speculative testimony often lapses into the conditional mode. *See, e.g.*, *id.* ¶ 105 (stating that "physicians who were participating in the ECOG 1496 and ECOG 4494 trials ***would have*** publicly discussed the ECOG 1496 and ECOG 4494 Protocols and disseminated at least the protocol schema" (emphasis added)). But regardless of how the statements are crafted, none of Dr. Grossbard's testimony regarding the ECOG protocols is based on personal knowledge. To cite one example among many, Dr. Grossbard has no firsthand knowledge that "The declaration of a protocol as 'active' marked the beginning of the period when the ECOG could provide the protocol to member institutions and . . . physicians at the member institutions could begin discussing the protocol and requirements of the trial with other physicians and patients." *Id.* ¶ 98.[8] Similarly, Dr. Grossbard states that ECOG 1496 and 4494 "***would have*** been readily obtainable from either ECOG (for ECOG physicians) or from ECOG physicians or

[8] Exhibits 1049 and 1050, which Dr. Grossbard cites in footnotes to this paragraph as evidence of the trial date and the first patient, provide no indication that the protocols were printed publications before the priority date. Dr. Grossbard does not suggest otherwise. Ex. 1002 ¶ 98 fns.79-80. It does not follow from the fact that ECOG physicians (e.g., the protocol authors) may have begun treating one or more patients that the protocol documents themselves were disseminated publicly and reasonably locatable. Dr. Grossbard's footnotes are simply non sequiturs.

from the NCI (for any physicians who may not have been a member of ECOG)," *id.* ¶ 104 (emphasis added), but Dr. Grossbard does not, and cannot, suggest that this is anything other than pure speculation, which is entitled to no weight.

Dr. Grossbard does testify that he was part of a ***different*** organization, the CALGB cooperative, *id.* ¶ 99, which was involved in the ECOG 4494 study. *See* Ex. 1004 at 2, top right corner (ECOG 4494 was also designated CALGB 9793). But he apparently has no knowledge of whether and to what extent the ECOG 4494 protocol was distributed even within CALGB, as he says nothing about it. Had the ECOG 4494 protocol in fact been widely distributed within CALGB, Dr. Grossbard presumably would have known about it.

Finally, although each of Exhibit 1003 and Exhibit 1004 contains both a cover memo and an attached protocol, neither Boehringer's petition nor Dr. Grossbard's declaration says anything about how—or, critically, ***when***—Boehringer obtained these memos and attachments. If the protocols actually had been widely disseminated before the filing date, as Boehringer claims, it is hard to imagine why Boehringer did not identify and rely on someone who could testify about receiving a copy of the protocols in the late 1990s (as opposed to Dr. Grossbard, who had no involvement with ECOG or the protocols). That Boehringer could obtain copies of these protocols when it filed its petition—sixteen years after the '172 patent was filed—proves nothing. Access to historical protocols nearly a decade after the study results were published (in 2006) provides no evidence whatsoever that the protocols were

publicly available before the filing date (in 1999). There is no competent evidence of record that anyone outside of ECOG, including Boehringer and Dr. Grossbard, actually obtained access to Exhibits 1003 and 1004 prior to the filing of the '172 patent. Boehringer has failed to establish that the protocols satisfy statutory requirements to be considered printed publications.

Because the ECOG protocols are not printed publications, Boehringer's anticipation argument and first four obviousness combinations—Pet. 31-32, 38-42—cannot be grounds for instituting trial. *See* 35 U.S.C. § 311(b). The petition's remaining six obviousness combinations are discussed next.

V. BOEHRINGER FAILS TO ESTABLISH A REASON TO COMBINE THE TEACHING OF PRIOR ART REFERENCES OR A REASONABLE EXPECTATION OF SUCCESS

To prove obviousness, Boehringer must show "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1068-69 (Fed. Cir. 2012).

The Federal Circuit has held that the field of biotechnology is "unpredictable." *See Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1055 (Fed. Cir. 2003). For such fields, "potential solutions are less likely to be genuinely predictable." *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Inc.*, 533 F.3d 1353, 1359 (Fed.

Cir. 2008). Boehringer has failed to meet its burden in each proposed obviousness ground, particularly given the unpredictable nature of this art.

A. McNeil (Ex. 1005) Alone

McNeil is a two-page news article that reports on an ongoing trial in elderly patients with ***intermediate-grade*** NHL (IG-NHL). The disclosure of using rituximab for maintenance therapy is found in a single sentence: "After initial therapy, patients who responded [to CHOP or R-CHOP[9] first-line chemotherapy] will be again randomly assigned to receive the maintenance regimen—Rituxan every 6 months for 2 years—or observation." Ex. 1005 at 1. McNeil fails to teach key claim limitations: (1) the use of rituximab maintenance therapy to treat ***low-grade*** NHL is not taught because the reported study is in IG-NHL patients, (2) rituximab maintenance therapy following ***CVP*** induction therapy is not taught because the reported study is using only CHOP-based induction therapy; and (3) rituximab maintenance regimen of ***four weekly doses of 375 mg/m^2*** is not taught because the article is entirely silent on the proper dosing for maintenance therapy.

McNeil also fails to provide any support for Boehringer's assertion that there was a reasonable expectation of success. First, McNeil reports only on the commencement of a study; it provides no results or data of any kind. Rather, it simply expressed hope that rituximab maintenance in that particular setting—following CHOP-based induction in patients with IG-NHL—would be a "***possible***

[9] "R-CHOP" refers to administration of rituximab (R-) along with CHOP.

improvement." *Id.* Boehringer never explains, much less offers evidence, why a skilled artisan reviewing McNeil would have any reasonable basis to believe rituximab maintenance therapy would work even in the reported study following CHOP-based induction in IG-NHL patients. And, indeed, McNeil's hope for a "possible improvement" turned out to be misplaced. The clinical study referenced by McNeil (which we now know was ECOG 4494) would show that the proposed rituximab maintenance therapy regimen was ***not*** effective after R-CHOP induction therapy in IG-NHL. *See* Ex. 1041 at abstract ("After R-CHOP, no benefit was provided by MR [rituximab maintenance].").

This failure to show efficacy with rituximab maintenance therapy in IG-NHL underscores the unpredictability in this field. As discussed in Section II.A.2. above, the field was replete with other maintenance-therapy failures, rebutting Boehringer's contention that a skilled artisan would have had a reasonable expectation of success in developing a successful maintenance treatment. *See Cyclobenzaprine* , 676 F.3d at 1081 ("[T]here can be little better evidence negating an expectation of success than actual reports of failure."). Particularly given this background of other failures, a news article announcing the start of yet another study cannot support an expectation of success.

Second, even assuming for the sake of argument that McNeil could have provided an expectation of success with its own regimen, McNeil differs materially from the claimed invention. It treats a different cancer, IG-NHL instead of LG-NHL, and uses a different induction therapy, CHOP instead of CVP. Whatever alleged

suggestion of success Boehringer draws from McNeil, there is nothing in McNeil (or elsewhere in the record) to suggest that a skilled artisan would believe that one could change the patient population ***and*** the induction therapy and still retain any alleged expectation of success. Boehringer simply resorts to unsubstantiated speculation. McNeil cannot support the weight of Boehringer's claims.

1. McNeil Does Not Provide A Reasonable Expectation Of Success For Using The Disclosed Rituximab Maintenance Regimen In LG-NHL

Given the unpredictability in the field and the fact that McNeil fails to provide any reasoning for its proposed rituximab maintenance regimen for IG-NHL, much less any results, McNeil would not have provided a reasonable expectation of success in a different disease: LG-NHL. *See Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 619 F.3d 1329, 1338 (Fed. Cir. 2010) (explaining that a prior art reference disclosing a "bare proposal to use" the drug raloxifene in one clinical setting "is insufficient to require a finding that an ordinary skilled artisan would have expected that a compound with known bioavailability issues—and known clinical failures—would successfully treat any human condition"). A skilled artisan would have recognized that responsiveness in IG-NHL cannot presumptively be applied to LG-NHL, discussed next.

a. *A Skilled Artisan Would Not Have Expected That The Rituximab Maintenance Regimen Studied In IG-NHL Could Be Successfully Applied To LG-NHL*

Skilled artisans knew that IG-NHL and LG-NHL responded differently to chemotherapy. *See, e.g.*, Ex. 2018 at 354 ("Patients with nodular histology [usually low

grade] have a significantly better response rate . . . than those with the corresponding diffuse [usually intermediate- and high-grade] involvement[.]"); Ex. 1011 at 2141 ("Non-Hodgkin's lymphomas . . . differ . . . in sensitivity to currently available chemotherapy"). As a result, LG-NHL and IG-NHL most often were treated with different chemotherapy regimens (although CHOP, an exception, was used for both). *Compare* Ex. 2001 at 1082, Table 111-7 *with id.* at 1084, Table 111-8. Skilled artisans knew that even with a response, relapses occurred sooner with IG-NHL than LG-NHL. *See* Ex. 2018 at 354 (finding that "[p]atients with diffuse histiocytic lymphoma demonstrated the highest rate of relapse during the first year of follow up, but late recurrence was uncommon. In contrast, the combined nodular histologic groups . . . demonstrated a pattern of continued relapse from remission over a 6-year period of follow up"). Skilled artisans knew that relapses occurred more often over time with LG-NHL than IG-NHL. Most patients with IG-NHL are cured with first-line chemotherapy (and therefore do not relapse). *See, e.g.,* Ex. 2001 at 1083 ("Most patients with intermediate- or high-grade lymphomas who achieve a complete remission with therapy may be cured."); Ex. 2019 at abstract, 1024 (finding that 76% of "patients with diffuse intermediate-grade [intermediate-grade] lymphoma" achieve CR and "overall risk of late relapse of those who attained CR was 6.8%"). In contrast, almost all patients with LG-NHL will continuously relapse until succumbing to the disease. *See, e.g.*, Ex. 1011 at 2142 ("[F]inal disease eradication cannot be achieved in low-grade lymphomas"); Ex. 1033 at 153-54 ("Relapse [] is the rule" for low-grade

lymphoma); Ex. 1024 at 1382 ("relapse rate remains high" for "low grade lymphoma").

Boehringer fails to provide a credible rationale why a skilled artisan would use McNeil's rituximab maintenance regimen for IG-NHL in a materially different cancer, LG-NHL. Instead, Boehringer simply asserts that a person of ordinary skill would have been motivated to use rituximab as maintenance therapy in LG-NHL and therefore "[o]ncologists would have been motivated to use the rituximab maintenance therapy method of ECOG 4494 [and McNeil]." *See* Pet. 39, 42. Boehringer ignores the differences between the two types of NHL and neglects to offer any explanation why a skilled artisan would believe that the rituximab maintenance regimen would work for both (and, in fact, it does not).[10] A similar situation was at issue in *Eli Lilly*, 619 F.3d 1329. There, the infringer argued that because the prior art suggested that the drug at issue could be used in one setting, autoimmune disorders, it would have been obvious to use it in another setting, osteoporosis. The Court rejected this argument because the infringer "was not able to show a credible connection between the" two different settings. *Id. at* 1338. Boehringer likewise has not done so here. As

[10] Boehringer argues that "interferon maintenance therapy was tested in more aggressive NHL before LG-NHL trials were conducted," Pet. 39, but offers no explanation why interferon use is a relevant surrogate for rituximab, a drug with an entirely different mechanism of action. *See also* Section V.C.2.

discussed in Sections A.1. and A.2. above, LG-NHL and IG-NHL are different cancers that respond differently to chemotherapy.

Similarly, in *Am. Hosp. Supply Corp. v. Travenol Labs., Inc.*, 745 F.2d 1 (Fed. Cir. 1984), the prior art was "directed to providing adequate nutritional support [using an amino acid product] to patients." *Id. at* 7. The claimed method at issue, however, was limited to a narrower subset of patients: those with liver disease. The court held that the claim was not obvious because it was "directed to a different class of users with specific unique nutritional problems." *Id.* Similarly, the claimed method here is for treating patients with LG-NHL, a unique type of lymphoma that is not curable and is characterized by constant relapse. McNeil discloses a rituximab regimen for a different set of patients, those with IG-NHL (a curable disease), and it does not render the claimed method obvious.

b. *The Art Discouraged Using Rituximab As Maintenance Therapy In LG-NHL Because Of Antigen Escape*

Boehringer's petition fails to address another reason why a skilled artisan would be skeptical about successfully using rituximab as maintenance therapy in LG-NHL: reported antigen escape in repeated treatments of LG-NHL with rituximab. Ex. 2020 at #2964. Antigen escape is a phenomenon whereby repeated use of rituximab causes cancerous cells to lose expression of CD20 and therefore become resistant to retreatment. It was first observed before the filing date of the '172 patent that the "potential for tumor transformation with loss of CD20 expression ***may prevent***

recurrent treatment." *Id.* (emphasis added). Because of this risk of antigen escape, a person of ordinary skill would have been skeptical about the success of rituximab as maintenance therapy.

In fact, before he was retained by Boehringer, and before the effective filing date of the '172 patent, Dr. Grossbard published his doubts that rituximab could be successfully used as maintenance therapy because of the antigen escape problem: "Maintenance therapy [with rituximab] is also being explored, ***although antigen escape may limit its use***." Ex. 2008 at 3696; *see also id.* at 3704 (same). Such uncertainty in the art precludes a reasonable expectation of success.

2. McNeil Taught Away From Omitting The Anthracycline Component Of CHOP, Doxorubicin.

McNeil discloses a rituximab maintenance regimen following an anthracycline-based induction therapy, *i.e.*, CHOP. By contrast, the claimed method does not use anthracycline—it is limited to a CVP. McNeil does not teach that the anthracycline of CHOP should (or could) be omitted. In fact, it teaches the opposite.

Even assuming for the sake of argument that McNeil's teachings would have been considered in connection with LG-NHL instead of IG-NHL, Boehringer must live with the entirety of McNeil's teachings, not just the cherry-picked sentences. *See Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed. Cir. 1987) (explaining that a prior art reference "must be considered in its entirety, i.e., as a whole, ***including portions that would lead away*** from the invention in suit" (emphasis added)). And

what McNeil teaches is the necessity of maintaining the anthracycline component of CHOP, *i.e.*, doxorubicin. In portions not cited by Boehringer's petition, McNeil describes a "recent, multicenter trial" where patients on an anthracycline-based combination regimen "did better than the same combination minus pirarubicin, which is an anthracycline similar to doxorubicin." Ex. 1005 at 267. McNeil concludes that this study "provides more support for the use of the stronger, antracyclin-based regimens." *Id.* This teaches away from the CVP therapy claimed in the '172 patent.

Despite the clear statement in McNeil that an anthracycline, such as doxorubicin, must be the backbone of chemotherapy, Boehringer argues that a skilled artisan reading McNeil would modify the disclosed CHOP regimen with CVP in part because "CVP had lower toxicity." *See* Pet. 39. Not so. McNeil teaches that reducing CHOP toxicity can be achieved by using "mini-CHOP," a regimen in which the "same drugs as CHOP [are] given in reduced doses along with supportive agent," thereby retaining doxorubicin. Ex. 1005 at 267. In other word, McNeil's solution to the "toxicity" issue is using an altered anthracycline-based regimen, rather than shifting to what it describes as clinically inferior regimens that lack anthracycline (such as CVP). Properly read as a whole, McNeil advocates for "the use of the stronger, antracyclin-based regimens," and thus discourages the skilled artisan from omitting the anthracycline doxorubicin.

Prior-art reports confirmed that combinations with rituximab and CHOP were highly effective in LG-NHL, further discouraging the skilled artisan from removing

doxorubicin. As Dr. Grossbard himself wrote, there was a *"**provocative**"* study in the prior art where the combination of rituximab and CHOP showed a "100%" response rate in LG-NHL: "One provocative study treated 38 patients with low-grade NHL . . . with Rituxan in combination with full-dose cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy . . . . The response rate was 100%, with about two thirds CRs." In that study, CHOP combination therapy was specifically chosen because it was effective in LG-NHL and because there was known synergy between rituximab and doxorubicin. *See* Ex. 2021 at 7 ("The standard CHOP regimen . . . was chosen for combination therapy with rituximab because . . . there is evidence of in vitro synergy between the antibody and doxorubicin."); Ex. 2023 at 550 ("CHOP chemotherapy was chosen because this cytotoxic regimen is an effective first-line therapy for low-grade or follicular NHL. The rationale for the combination of rituximab and CHOP includes . . . in vitro synergy with certain cytotoxic drugs (including doxorubicin)."). Thus, a skilled artisan would not have modified the protocol described in McNeil by omitting doxorubicin even assuming, for the sake of argument, that a skilled artisan would have believed that McNeil's IG-NHL maintenance regimen was applicable to LG-NHL.

Tellingly, Boehringer has not cited a single study where rituximab was given after CVP chemotherapy in non-relapsed patients. Instead, Boehringer relies solely on the testimony of Dr. Grossbard that it allegedly would have been obvious to substitute CVP for the CHOP induction therapy taught by McNeil. *See* Pet. 36-37.

That testimony relies entirely on the assertion that "CVP was standard induction for LG-NHL" because it was less toxic than CHOP. *See* Ex. 1002 ¶ 121. But as the Federal Circuit has explained, a claimed combination (such as CVP induction with rituximab maintenance) is not obvious simply because one or both components of the combination were "routinely prescribed." *See In re Brimonidine Patent Litig.*, 643 F.3d 1366, 1374 (Fed. Cir. 2011) (finding claimed combination was non-obvious even when both components were "routinely prescribed together.").

As both Boehringer and Dr. Grossbard admit, "CHOP [] was used to induce remission in LG-NHL patients." Ex. 1002 ¶ 41; *see also* Pet. 41. And as discussed, in the "provocative" prior art study, LG-NHL was treated with the combination of CHOP and rituximab specifically because of the known synergy between rituximab and doxorubicin. Simply put, nothing in McNeil suggests that the doxorubicin component of CHOP could or should be omitted. Rather, McNeil's teachings reinforce that the skilled artisan should use CHOP-based induction followed by rituximab maintenance, not the claimed CVP induction.

3. McNeil Fails To Disclose The Claimed Rituximab Maintenance Dosing Of 4 Weekly Infusions Of 375 mg/m^2

Lastly, McNeil fails to disclose rituximab maintenance therapy given as four weekly 375 mg/m^2 infusions every six months for two years. McNeil states that the maintenance regimen studied was "Rituxan every 6 months for 2 years," Ex. 1005 at 1, but there is no disclosure that each dosing regimen should be four weekly doses

of 375 mg/m^2. Boehringer relies entirely on an assertion that this dosing regimen would have been obvious because four weekly infusions of 375 mg/m^2 was the FDA-approved dosing regimen to treat ***relapsed*** disease. But, as discussed in the next Section, a skilled artisan would not have used the rituximab dosing regimen to treat relapsed disease as the dosing regimen for maintenance therapy, and Boehringer offers no contrary evidence.

B. McNeil (Ex. 1005) In Combination with Rituxan Label (Ex. 1008)

Boehringer cites the 1997 Rituxan Label in an effort to fill the dosing hole in McNeil, arguing that the label disclosed the "standard rituximab dosing regimen." *See* Pet. 42; Ex. 1002 ¶ 129. But the label only recommended the regimen of four weekly doses of 375 mg/m^2 for treatment of relapsed or refractory low-grade or follicular NHL. Indeed, that was the only approved indication. Boehringer offers no evidence or rationale why a person of ordinary skill would believe the dosing regimen for relapsed or refractory disease would be appropriate for maintenance therapy.

In fact, the data presented in the label affirmatively suggests not using the relapsed dosing regimen in a disease setting where there will be a lower tumor burden and fewer circulating B-cells in the patient, such as what might encountered in a maintenance treatment setting. In such a setting, the label suggests use of a ***lower*** dose. The pharmacokinetic section of the label explains that rituximab serum level is higher when there are fewer circulating B-cells and less tumor burden, as would be the situation for a patient receiving maintenance treatment. *See* Ex. 1008 at 1 ("The peak

and trough serum levels of Rituximab were inversely correlated with baseline values for the number of circulating CD20 positive B cells and measures of disease burden.").[11] Indeed, Boehringer's petition acknowledges that tumor burden and B-cell levels are lower in the maintenance setting, where rituximab would be repeatedly given after induction. *See* Pet. 12-13 ("A patient with a CR or PR will have a lower tumor burden relative to that which existed prior to the CVP chemotherapy."), *id.* at 25 ("administration of RITUXAN resulted in a rapid and sustained depletion of circulating and issue-based B cells").

Given the label's description of the pharmacokinetic profile of rituximab, a skilled artisan would not have modified the maintenance schedule proposed by McNeil to use the relapsed dosing regimen of four weekly doses of 375 mg/m^2. If anything, that person would have used less rituximab, either by decreasing the frequency (less than four doses) or the amount (mg/m^2) given in each administration.

In the face of the label's data suggesting that the dose for relapsed disease would not be appropriate in the maintenance setting, Boehringer cites only the unsupported opinion of Dr. Grossbard to argue otherwise. *See* Pet.42-43, *citing* Ex.1002 ¶ 130. Dr. Grossbard offers no explanation, and cites no evidence, for his

[11] This is due to a phenomenon known as "tumor sink," whereby tumor cells would sequester the rituximab and reduce its effective serum concentration. *See* Ex. 1007 at 72:5-9, 78-79.

assertion that the four weekly 375mg/m^2 dosing would be used or would be "expected to succeed." The Board need not credit such conclusory assertions. *See* 37 C.F.R. § 42.65(a); *Atoptech, Inc. v. Synopsys, Inc.*, IPR2014-01150, Paper 11 at 17-18 (Jan. 21, 2015) (not crediting expert declaration that "lacks any evidence to support the Petition's conclusions, and indeed, simply repeats verbatim the Petition's conclusions in each instance."). Boehringer's conclusion that "it would have been obvious to continue using the same dosage of the same drug to treat the same disease," without any analysis, or any discussion of the differences between the treatment of naïve or relapsed and maintenance therapy, is indicative of the petition's impermissible hindsight-driven approach to obviousness. Obviousness "cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013).

C. McNeil (Ex. 1005), Alone or In Combination with Rituxan Label (Ex. 1008), In Combination with Unterhalt (Ex. 1006)

Boehringer also tries to fill the holes in McNeil by using Unterhalt, an abstract reporting preliminary results of a study using ***interferon*** maintenance therapy in LG-NHL. Boehringer contends that this abstract would have provided a reasonable expectation of success for ***rituximab*** maintenance therapy because Unterhalt states that ***interferon*** maintenance can result in "significant prolongation of DFS [disease-free survival]." Pet. 41. Boehringer's argument lacks any scientific credibility—

interferon has an entirely different mechanism of action than rituximab, and a person of skill would not equate the two agents. Moreover, because Unterhalt is a short abstract reporting preliminary results, it would not have overcome prior-art studies showing that interferon ***failed*** as maintenance therapy. And Unterhalt provides no insight into other claim limitations missing from McNeil, including use of CVP induction before rituximab maintenance, or the claimed rituximab dosing.

1. A Skilled Artisan Would Not Think That Allegedly Successful Interferon Maintenance Therapy Indicates That Rituximab Maintenance Therapy Would Be Successful.

Interferon is a naturally-occurring cytokine, *i.e.*, signaling compound, that triggers the protective defenses of a person's immune system. It is in a class (cytokine) different from rituximab (monoclonal antibody) and works against lymphomas using an entirely unrelated mechanism of action. Interferons "improve a cancer patient's immune response against cancer cells," Ex. 1027 at 2, while rituximab targets and kills cancerous B cells (and, in doing so, can weaken the immune system by collaterally killing normal B cells). Ex. 1008 at 1, left column.

Boehringer has cited nothing more than unsupported expert opinion to argue that any so-called success with interferon would have led a person of ordinary skill to have a reasonable expectation of success using rituximab in maintenance therapy. *See* Pet. 44. The sole basis of Dr. Grossbard's opinion seems to be that interferon and rituximab are both "biologics" that have been used to treat NHL. *See* Ex. 1002 ¶ 131. But the category of "biologics," a.k.a. "biological response modifiers" (BRM), is vast

and diverse. *See* Ex. 1027 (BRMs include categories of "interferons, interleukins, tumor necrosis factor, colony-stimulating factors, monoclonal antibodies, and cancer vaccines"). A skilled artisan would not have thought that clinical results observed with one biologic product could be translated into results for other biologics, particularly those known to have unrelated mechanisms of action. And indeed, Boehringer and Dr. Grossbard have no explanation (and cannot credibly explain) why the clinical efficacy of a cytokine such as interferon (or for that matter, a vaccine such as BCG) would cause a person of ordinary skill to believe that any monoclonal antibody, let alone a monoclonal antibody targeting CD20 such as rituximab, would be an effective maintenance therapy. The Board should reject Boehringer's attempt to equate disparate classes of biologic drugs.

2. Unterhalt Reports Only Preliminary—Not Final—Results And Would Not Have Overcome The Many Prior Art Studies Showing Interferon Failed As Maintenance Therapy.

Boehringer presents no evidence of genuine success with interferon maintenance. Unterhalt itself recognized that its preliminary results contradicted the widely held belief that interferon maintenance therapy was unsuccessful with long-term follow-up. *See* Ex. 1006 ("an increased relapse rate is usually noted within six to twelve months after the end of IFN therapy resulting in the merge of disease free and overall survival curves."). In fact, many prior art studies found interferon to be unsuccessful as maintenance therapy in LG-NHL. *See, e.g.*, Ex. 1067 at abstract ("To date, no additional benefit has been seen from the administration of IFN for

maintenance.");[12] Ex. 2024 at *10; Ex. 2025 at *48; Ex. 2026 at abstract; Ex. 2014 at 2220 (meta-analysis of pre- and post-filing-date clinical studies finding that "no significant effect [was seen] in studies in which [interferon] was given only as maintenance."). Thus, contrary to Boehringer's assertion, interferon had not been successful as maintenance therapy in patients with LG-NHL.

A skilled artisan would not have viewed the preliminary results reported in the Unterhalt abstract as changing these general beliefs. In fact, Dr. Grossbard was editor of a textbook describing the Unterhalt study as showing no statistically significant improvement in outcomes. Ex. 2027 at 100, Table 6-5 (citing a later Unterhalt *et al.* publication about the same study [Ex. 2028 at 1801]). Unterhalt, against the backdrop of repeated failures using interferon maintenance therapy in LG-NHL, thus, would not have established a reasonable likelihood of success of using interferon in maintenance therapy, let alone an entirely different biologic drug like rituximab.

D. McNeil (Ex. 1005), Alone or In Combination with Rituxan Label (Ex. 1008), In Combination with the 1997 FDA Transcript (Ex. 1007)

Boehringer also attempts to fill the holes in McNeil using the transcript of an FDA hearing on the then-pending approval of rituximab to treat relapsed LG-NHL (1997 FDA Transcript).

As a threshold matter, Boehringer has failed to establish that the FDA

[12] Boehringer and Dr. Grossbard mistakenly characterize Ex. 1067 as establishing benefits for additional interferon maintenance. Pet. 19-20; *see also* Ex. 1002 ¶ 66.

Transcript was publicly accessible before August 11, 1999, and thus is a prior art printed publication. Boehringer relies entirely on its expert's speculation that "The FDA Transcript ***would have*** been publicly available to any interested person from the FDA prior to the Cut-off Date, and the FDA Transcript itself indicates that it was publicly available at least by August 8, 1997." Ex. 1002 ¶ 82; *see* Pet. 23. Dr. Grossbard provides no explanation as to why he is qualified to offer an opinion as to whether the FDA Transcript was publicly available. Dr. Grossbard does not claim he worked at the FDA, has any personal familiarity with FDA procedures, attended the hearing, or even received a copy of the 1997 FDA Transcript other than in connection with his work for Boehringer in this IPR. He appears to surmise that it "would have been publicly available" prior to the filing date because it now can be downloaded from the FDA website, sixteen years later. That is not an expert opinion; it is rank speculation. Dr. Grossbard also assumes that the date stamp of "97 Aug-8" indicates when a copy was "publicly available," but offers no indication that he has any personal knowledge or other basis to make this assertion. The date stamp could have been, for example, the date the FDA received the transcript from the court reporting service, which says nothing about when the transcript was made publicly available. Likewise, the hearing may have been public, but that does not reveal when the transcript, which is the alleged printed publication, was made publicly available. *A.R.M., Inc. v. Cottingham Agencies Ltd.*, IPR2014-00671, Paper 10 at 6-8 (P.T.A.B. Oct. 3, 2014) (finding that while petitioner offered evidence that an amusement park ride was "available to

public," petitioner failed to show that a document depicting the ride was "available as prior art for purposes of *inter partes* review"). Boehringer's lack of competent evidence is dispositive, and the Board should reject its characterization of the FDA transcript as a printed publication.

Even assuming, for the sake of argument, that the FDA Transcript is a printed publication, it does not supply any of the missing elements absent in the combination of McNeil and the 1997 Rituxan Label (Ex. 1008). The FDA Transcript does not teach that rituximab should be used as maintenance therapy in LG-NHL. It gives no guidance on how to dose rituximab in maintenance therapy for LG-NHL. And it does not suggest that doxorubicin should be omitted from CHOP.

The FDA Transcript does not even mention maintenance therapy. This is not surprising, as the hearing concerned whether rituximab should be approved as therapy in certain types of active disease—relapsed or refractory lymphoma. *See* Ex. 1007 at 17; *see also* Ex. 1002 ¶ 84 (Dr. Grossbard admits that the "patients studied by Dr. Grillo-López and colleagues were ***relapsed and refractory***" (emphasis added)). Consequently, a person of ordinary skill would not have found anything in the transcript suggesting any modification to McNeil's rituximab maintenance regimen in IG-NHL, much less a reasonable likelihood of success.

Boehringer argues that the FDA Transcript would have motivated a skilled artisan to practice the claimed rituximab maintenance regimen of four weekly 375 mg/m^2 doses every six months for two years because it allegedly "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)." Pet. 45. This is not what the FDA Transcript teaches. Instead, Boehringer divines this theory using anecdotal stories in the hearing transcript about patients who have received multiple courses of rituximab due to ***multiple relapses***. *See, e.g.*, Pet. 23; Pet. 41-42.

These anecdotes would not have given a skilled artisan a reasonable expectation of success to practice the claimed rituximab maintenance regimen. First, a skilled artisan would not give weight to unpublished, anecdotal stories. As the FDA recently cautioned, "public health often is not well served when those judgments rest on anecdotal experience . . . too often, the promise of safety and effectiveness made by such sources has not been demonstrated when adequate and well-controlled clinical studies are completed." Ex. 2015 at 2.

Second, none of these patient stories described the use of rituximab maintenance therapy following responsive induction therapy. Rather, they concerned patients who had multiple courses of treatment with rituximab due to ***multiple relapses***. The FDA Transcript is simply cumulative of other art, including that cited in prosecution, showing use of rituximab in patents who relapsed. But that remains a very different indication than maintenance therapy in responsive patients, which the patent claim requires and about which the FDA Transcript is silent.

Third, none of these anecdotes described the administration of rituximab as

frequently as every six months. Indeed, some stories spoke of retreatment after "20 months or more." Pet. 42. Boehringer fails to explain how this would provide any expectation of success, lacking in McNeil, for dosing rituximab every six months for two years as a maintenance treatment of LG-NHL.

Lastly, because there is no discussion of using rituximab as maintenance therapy in the FDA Transcript, there is also no teaching of which induction therapy should precede rituximab maintenance. The FDA Transcript therefore fails to provide any reason for a skilled artisan to modify the CHOP induction of McNeil to arrive at the claimed CVP induction therapy.

E. McLaughlin (Ex. 1009) Alone

McLaughlin is a research article reporting the use of rituximab to treat relapsed LG-NHL. A compilation of the McLaughlin article along with abstracts of other rituximab studies was submitted to the Patent Office as the provisional application for the '172 patent. Boehringer argues on the one hand that "[n]othing in that compilation [including McLaughlin] describes the specific combination claimed in the '172 patent," and, on the other hand, argues that McLaughlin alone renders the '172 patent obvious. *Compare* Pet. 9 *with* Pet. 45. Boehringer's lack of consistency belies the weakness of this obviousness ground.

McLaughlin is limited to the study of patients with ***relapsed*** LG-NHL, and does not teach material claim limitations: (1) the use of rituximab maintenance therapy, (2) rituximab maintenance therapy following CVP induction therapy, and

(3) rituximab maintenance regimen of four weekly doses of 375 mg/m^2 every six months for two years.

1. McLaughlin Does Not Suggest That Rituximab Maintenance Therapy In LG-NHL Would Be Successful.

Boehringer argues that "[o]ne of ordinary skill would have concluded from [McLaughlin] that rituximab was more effective in patients with a lower tumor burden at the time of rituximab therapy" (Pet. 27). Boehringer is wrong.

Boehringer contends that McLaughlin "explicitly encourages the use of rituximab maintenance therapy in a CR." Pet. 27 (quoting Ex. 1009 at 2831). But Boehringer's cited quote from McLaughlin says no such thing. McLaughlin states that "the use of [rituximab] in a minimal or subclinical disease setting is a consideration." *Id.* at 2831. As explained above in Section III.C., and as Dr. Grossbard himself has written, "maintenance therapy" is recognized as being different from treatment in the "minimal disease setting." Ex. 2008 at 3704. Moreover, McLaughlin merely says that use of rituximab in that minimal disease setting "is a consideration." Such a noncommittal statement is not an explicit encouragement and does not establish a reasonable expectation of success. *See Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 997 (Fed. Cir. 2009) (explaining that reasonable expectation of success requires more than "general guidance [in a prior art reference] as to the particular form of the claimed invention or how to achieve it.").

Boehringer also contends that McLaughlin teaches that rituximab worked better in relapsed patients who had responded to their last round of chemotherapy. *See* Pet. 27 (quoting Ex. 1009 at 2827). In fact, the cited statement in McLaughlin suggests the opposite; the study showed that to the extent those patients had any better responses, the differences were "***nonsignificant***." A skilled artisan would not interpret a statistically insignificant result from one treatment setting (therapy after relapse) as suggesting that rituximab would be successful in a different setting—treating responders, prior to relapse, for the purpose of preventing relapse.

2. McLaughlin Taught Away From Omitting Doxorubicin

Boehringer fails to explain how McLaughlin allegedly suggests using CVP induction therapy before rituximab maintenance. Boehringer asserts that patients in McLaughlin were "treated with chemotherapy (including necessarily CVP)," Pet. 45, even though CVP is not mentioned anywhere in McLaughlin. Dr. Grossbard tacitly acknowledges as much: He asserts that, because CVP had "previously been used" (i.e., in other studies) as front-line therapy, then "at least some" of the McLaughlin patients must have received CVP. Dr. Grossbard's assertion is speculative and legally insufficient. In trying to transform a reference that is entirely silent about CVP into one that purportedly suggests its use, Boehringer essentially argues, *sub silentio*, that CVP is inherently disclosed in McLaughlin. But to surmise that "at least some patients" probably would have received CVP therapy comes nowhere near the strict requirements for inherent disclosure. *Allergan, Inc. v. Apotex, Inc.*, 754 F.3d 952, 960

(Fed. Cir. 2014) (finding no inherency because "[i]nherency may not be established by probabilities or possibilities"); *Ex Parte May*, Appeal No. 1999-0941, 1999 WL 33224337, at *2 (B.P.A.I. Jan. 1, 2009) ("[A] showing of likely or probable inherency is not sufficient to support a rejection under 35 U.S.C. § 102 or 103 under the theory of inherency.")

Not only is CVP absent, but on closer read, McLaughlin teaches that CHOP with rituximab should be used in patients with LG-NHL because the regimen showed good response without increasing toxicity. *See* Ex. 1009 at 2831. This encouragement from McLaughlin and others to use CHOP with rituximab (*see* Section V.A.2. above), would have discouraged the skilled person from omitting doxorubicin.

3. McLaughlin Does Not Teach That "four weekly administrations of rituximab at a dose of 375 mg/m^2" Should Be Used For Maintenance Therapy.

Boehringer fails to explain how McLaughlin would lead a skilled artisan to use its relapse-dosing scheme for maintenance therapy. As discussed in Section V.B., a skilled artisan would have lowered the dose of rituximab in the setting of maintenance therapy in light of the reduced B-cell levels and tumor burden in such patients.

4. Boehringer Relies On Hindsight To Argue That Rituximab Maintenance Dosing Should Be Given "every six months."

Boehringer asserts that McLaughlin would have motivated a skilled artisan to practice the claimed rituximab maintenance schedule of "every six months" because

McLaughlin taught that "a course of rituximab resulted in rapid depletion of B-cells and recovery of the B-cells did not occur until 6 months later." Pet. 48.

To make this argument, Boehringer relies entirely on retracing with hindsight the steps taken by the inventor. Boehringer relies on the ***current*** Rituxan® webpage to explain why McLaughlin allegedly would have motivated a skilled artisan to schedule rituximab maintenance for every six months, even going so far as to argue that Biogen's current webpage is a "concession" of obviousness. *See* Pet. 46. This is classic impermissible hindsight. *See Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art.").[13]

Boehringer relies on hindsight because nothing in the prior art suggested that B-cell recovery time should dictate the frequency of giving rituximab maintenance doses. The purpose of maintenance therapy was to prevent tumor regrowth, and a

[13] Boehringer also argues that the six-month schedule would have been obvious because the authors of Hainsworth (Ex. 1043), an article that post-dates the invention and is not prior art, "***independently*** devised the identical rituximab maintenance protocol." Pet. 38 (emphasis added). This unsupported assertion is belied by the fact that the Hainsworth study was 'supported in part by [a] grant . . . from Genentech, Inc.," a co-developer of rituximab with Biogen. Ex. 1043 at 4261.

person of ordinary skill therefore could have, for example, designed a dosing regimen based on the duration of response seen in McLaughlin, approximately 13 months. Ex. 1009 at 2827. Alternatively, dosing could have matched the duration of rituximab's tumor reduction effects, which were known to last up to 16 months. Ex. 1007 at 40:5-11. Boehringer and its expert point to no reason or prior art support for their claim that rituximab should have been dosed to sustain B-cell depletion, *i.e.,* every six months, in the maintenance setting. *See* Pet. 48; Ex. 1002 ¶ 133. Boehringer's rationale comes only from Biogen's publications that long post-date the patent.

Tellingly, even by 2002, four years after McLaughlin was published, Dr. Grossbard wrote that "[f]urther study is needed to establish treatment schedules [for rituximab], such as maintenance therapy after remission induction." Ex. 2027 at 304. This post-invention statement by Boehringer's own expert belies the argument that a person of ordinary skill would have found it obvious to give rituximab every six months for maintenance at the time of the invention.

F. McLaughlin (Ex. 1009) In Combination with McNeil (Ex. 1005)

As discussed above in Section V.A., like McLaughlin, McNeil fails to teach any of the material limitations of the claims: (1) the use of rituximab maintenance therapy to treat LG-NHL, (2) rituximab maintenance therapy following CVP induction therapy, and (3) rituximab maintenance regimen of four weekly doses of 375 mg/m^2 every six months for two years. Neither McLaughlin nor McNeil fills in any of the missing claim limitations for the other.

Boehringer argues that McLaughlin would have motivated the use of McNeil's rituximab maintenance regimen for LG-NHL. Pet. 48. This argument fails because McLaughlin does not encourage the use of rituximab as maintenance therapy for LG-NHL, as discussed in Section V.E.1. Moreover, even if McNeil's regimen could be applied to LG-NHL, the claimed method would still be non-obvious. McNeil teaches the use of CHOP, not CVP, induction therapy; and McNeil does not disclose the dosing scheme of "four weekly doses of rituximab at 375 mg/m^2." *See* Sections V.A.2. and V.A.3. McLaughlin does not fill in these missing claim elements. McLaughlin says nothing at all about CVP, and in fact discourages the omission of doxorubicin by explaining that the addition of rituximab to CHOP in an ongoing study showed good response without increasing toxicity. *See* Section V.E.2. Nor does McLaughlin teach that its relapse-dosing regimen of "four weekly doses of rituximab at 375 mg/m^2" should be used as the maintenance dosing regimen. *See* Section V.E.3.

Boehringer cannot fix deficiencies in one reference by combining it with another reference suffering from the same shortcomings. Nor can Boehringer prove obviousness by picking and choosing bits from different prior art references and combining them with the benefit of hindsight, which is all Boehringer offers here. *See Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011) ("Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination.").

VI. BOEHRINGER FAILS TO OVERCOME THE OBJECTIVE EVIDENCE OF NON-OBVIOUSNESS

Boehringer's petition also should be denied because it fails to rebut Biogen's objective indicia of non-obviousness presented during examination. The Office credited this evidence of unexpected success and long-felt need, which Boehringer's petition fails to overcome.

A. There Existed A Long-Felt Need To Prevent Relapse in LG-NHL

During examination, Biogen presented evidence showing there was long-felt need to prevent relapse in LG-NHL. Ex. 1064 at 8. Citing Hochster (Ex. 1040), Biogen explained that "no single chemotherapy regimen has been considered to provide a definitive progression-free survival (PFS) or overall survival (OS) advantage" for LG-NHL in the prior decades. Ex. 1064 at 8. Indeed, as discussed in Sections II.A.2. and V.C.2. above, prior art attempts using maintenance therapy with standard chemotherapy and other biologics were unsuccessful in LG-NHL. And Boehringer itself has acknowledged that there was long-felt need. *See* Pet. 18 ("It was widely understood for at least 10 years before the priority date of the '172 patent that the malignant B-cells of LG-NHL are very difficult to completely eliminate."). This long-felt need for therapy that could provide a definitive improvement in progression-free survival with minimal toxicity in LG-NHL was satisfied by the claimed invention, which became the "new standard" for patients with low-grade lymphoma, as discussed further below. Ex. 1040 at 7.

B. The Claimed Invention Produced Unexpected Results

In its notice of allowance, the Patent Office credited the unexpected results shown in Hochster (Ex. 1040). *See* Ex. 1069 at 2. Hochster is a peer-reviewed paper reporting on clinical trials of the claimed invention. The claimed treatment resulted in "prolongation of PFS for MR-treated patients with a median more than three times longer (4.3 v. 1.3 years)" in patients with LG-NHL. Ex. 1040 at 5. It also "significantly prolong[ed] PFS, ***to a far greater extent than achieved by any prior strategy and with minimal toxicity***." Ex. 1040 at 7 (emphasis added). These results were unexpected because no treatment in the prior decades had shown definitive survival improvement for LG-NHL: "during a 30-year period of study, no single chemotherapy regimen has been considered to provide a definitive progression-free survival (PFS) or overall survival (OS) advantage." Ex. 1040 at 1607; *see also Ex.* 2017 at 317 ("The therapeutic approach to low-grade NHL . . . remains controversial. The major controversy is whether ***any*** treatment can induce long-term disease-free survival and alter the natural course of the disease."). Because of the drastic improvements in progression-free survival and low toxicity, the claimed treatment regimen became the "new standard" for patients with low-grade lymphoma, fulfilling the long-felt need. Ex. 1040 at 7.

Boehringer's response is unpersuasive. Boehringer first argues that the Hochster results were not unexpected because its authors wrote: "Our study confirmed the hypothesis that rituximab would be an effective and safe maintenance

after CVP chemotherapy." Pet. 57. Boehringer's argument presumes, without evidentiary support, that "the hypothesis" referred to in Hochster was shared by persons of ordinary skill prior to the time of the invention and not merely the assignee and its collaborators. Moreover, proving and disproving a "hypothesis" has long been part of the vernacular of clinical trial design. *See generally* Ex. 2022. Using the word "hypothesis" in a clinical report hardly suggests that a person of ordinary would have reasonably expected certain results.

Boehringer next argues that the Patent Office should have evaluated the progression-free survival improvements from the claimed method against "CVP induction followed by other forms of maintenance therapy that had been used to treat LG-NHL, e.g., IFN maintenance therapy." Pet. 57. This argument fails because (1) the Patent Office was aware of studies evaluating interferon (IFN) maintenance therapy, and (2) a no-maintenance arm was the proper control because, due to numerous failures of others in developing successful maintenance therapy, "[m]aintenance therapy [was] rarely employed in non-Hodgkin's lymphoma once a clinical complete response has been obtained." *See* Ex. 2003 at 912.

Contrary to Boehringer's representation (Pet. 4), the Office did review studies using interferon maintenance therapy. *See* Ex. 2007 at 7, 15, 25 (listing three IDS references, D100, D200, and D338, that were studies evaluating interferon maintenance therapy in LG-NHL, including Exs. 1067 and 1034 cited by Boehringer's petition). Hochster also mentions interferon maintenance studies, and concludes that

interferon would not have been a proper control because interferon "was not widely adopted due to the need for continuous administration, poor tolerance, and modest benefit." Ex. 1040 at 1. Thus, the Office was fully aware of interferon maintenance study results when finding that the claimed method of treating LG-NHL showed unexpected success.

Boehringer thus has failed to rebut the objective indicia of non-obviousness upon which the Patent Office relied to find the claimed method patentable.

VII. CONCLUSION

For the reasons set forth above, Biogen respectfully submits that the Board should deny Boehringer's petition for *inter partes* review in its entirety.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, the undersigned certifies that on April 15, 2015, a copy of the foregoing document **BIOGEN, INC.'S PATENT OWNER PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107** has been served in its entirety via e-mail on counsel of record for petitioners at the following address:

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