UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.
Petitioner,

v.

BIOGEN, INC.
Patent Owner.

Case IPR2017-01093
U.S. Patent No. 8,329,172

PATENT OWNER PRELIMINARY RESPONSE

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I. INTRODUCTION

Petitioner Celltrion, Inc. repeats arguments already considered and rejected by the Board in an prior *inter partes* review (IPR2015-00418) of the same patent, U.S. Pat. 8,329,172 (the "'172 patent"). Of the references that constitute Petitioner's Grounds, all but three were previously raised. And even these three—Grossbard (Ex. 1010), Bishop (Ex. 1006), and Dana (Ex. 1007)—are cumulative of references that were previously found unpersuasive by the Board. There is no new evidence here that warrants a different outcome. The Board should again deny *inter partes* review.

Like the prior petition, the principal patentability challenge here, in Grounds 1 and 2, relies on what Petitioner describes as copies of a protocol and patient consent form for a clinical study, E1496, coordinated by the Eastern Cooperative Oncology Group (ECOG). The Board previously held there was insufficient evidence that these documents were publicly available "printed publications." That remains true.

For Ground 1 and the "Suggested Patient Consent Form" (Ex. 1008), Petitioner relies on the statement of its proposed expert, Dr. Walter Longo, an oncologist at a hospital affiliated with ECOG, that he "distribute[d] the [E1496 patient consent] form to approximately 40 prospective patients." Ex. 1002, ¶49.

Critically, however, neither petitioner nor Dr. Longo says ***when*** such distribution allegedly occurred. Petitioner's own evidence shows that only one patient was enrolled in the study at Dr. Longo's hospital before the priority date, and Dr. Longo does not claim that he personally enrolled or treated that patient and can only speculate what consent form was given.[1] That Dr. Longo may have distributed a consent form "to approximately 40 prospective patients" ***after*** the priority date is of no help to Petitioner. Moreover, even assuming competent testimony that one patient received a copy of Exhibit 1008 before the priority date, this would still not establish it as a printed publication. *See Preemption Devices, Inc. v. Minnesota Mining & Mfg.*, 732 F.2d 903, 906 (Fed. Cir. 1984) (finding that mailing multiple copies of a document to a single recipient does not transform the document into a printed publication where "[t]here is no evidence to show further dissemination by the [recipient] before the critical date"). Finally, even if Exhibit 1008 was given to a patient, there is still no evidence that a non-ECOG ***skilled artisan*** received it before the priority date.

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[1] As discussed in Section IV.A.2, Exhibit 1008 appears to be another document's "Appendix" that merely includes language for a "***Suggested*** Patient Consent Form." Ex. 1008, 001.

For Ground 2 and the "E1496 Protocol" (Ex. 1009), Petitioner relies on an ECOG webpage that the Board previously held was insufficient to establish public accessibility because the website was not searchable and did not provide access to the protocols. Non-Institution Decision, IPR2015-00418, Paper 14 (July 13, 2015) (Ex. 2001) at 12-13. Petitioner's expert declaration does not cure the problem. Dr. Longo offers only speculative testimony that his hospital "would" have made the protocol available to "any inquiring physician." Ex. 1002, ¶57. Critically, however, Dr. Longo does not testify to a single inquiry from an outside doctor. This is fatal to Petitioner's argument. *See Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1330 (Fed. Cir. 2004) (holding 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.").

Even assuming Exhibits 1008 and 1009 are printed publications, anticipation Grounds 1 and 2 still fail because neither document discloses every claim limitation. As the Board held previously, the claim limitation of, "to which the patient responds," requires the patient to "respond[] according to the criteria set forth in the '172 patent…[which provides] specific criteria for a complete response (CR) and a partial response (PR)…." Ex. 2001, 006. Nothing in Exhibits 1008 and 1009 discloses the response required by the claim. Petitioner tries to sidestep

this deficiency by pointing to the words "regresses," "not progressed," and "maintenance" in the documents. Pet. 39-40. But Petitioner is unable to show that those words describe the response required by the claims (and indeed, does not even try), thus falling far short of the "strict identity" requirement for anticipation. The documents either contain no discussion of what constitutes a clinical response (Ex. 1008), or define partial and complete responses in ways that are substantially different from the claim limitation (Ex. 1009). In either case, the lack of identity between the prior art and the requirements of the claims is fatal to anticipation.

With respect to Petitioner's obviousness Grounds 3 and 4, both fail at the outset because Petitioner offers no supporting evidence that Ex. 1004, a purported copy of a Rituxan® label, was a publicly accessible "printed publication." *See Mylan Pharms. v. Boehringer Ingelheim Int'l GmbH*, IPR2016-01566, Paper 15, at 11-12 (Feb. 3, 2017) (holding that a purported drug label did not "qualif[y] as prior art under 35 U.S.C. §102(b)" without supporting evidence of public accessibility).

Even assuming Ex. 1004 is a printed publication, Grounds 3 and 4 still fail because none of the references teaches a material limitation of the claim: a rituximab maintenance regimen of four weekly doses of 375 mg/m^2 every six months for two years in low-grade lymphoma (LG-NHL). In an attempt to fill in

this gap, Petitioner simply pieces together disparate portions of different references for each claim element, providing little, if any, reasoning as to why a skilled artisan would have combined such references, or why the artisan allegedly would have had a reasonable expectation of success in doing so.

For both Grounds 3 and 4, Petitioner asserts, for example, that a skilled artisan would have used the rituximab dosing regimen approved to treat ***relapsed*** disease as the dosage for ***maintenance*** therapy, which is designed to maintain a response in the absence of relapse. Petitioner provides no new evidence that should alter the Board's prior finding that "relapsed patients…are beyond the scope of claim 1," Ex. 2001, 018, and that the evidence "does not demonstrate that a skilled artisan would have understood that those dosages [in relapsed disease] were necessarily given" in a maintenance setting. *See id.*, 021.

Petitioner also argues for both Grounds 3 and 4 that skilled artisans would have applied a dosing regimen being studied in elderly patients with aggressive lymphoma to the claimed population—patients with low-grade lymphoma.[2] But

[2] "[I]ntermediate- or high-grade lymphomas…[are] referred to as the aggressive lymphomas to distinguish them from the indolent or low-grade histologies." Ex. 1017, 030.

again, Petitioner provides no new evidence that should alter the Board's prior finding that disclosures related to aggressive lymphomas do not apply to low-grade lymphoma, or vice versa. *See, e.g.*, Ex. 2001, 021 ("[That] the FDA-approved/recommended weekly rituximab dosage for relapsed or refractory LG-NHL might be the same as the dosage recited in claim 1 does not demonstrate that a skilled artisan would have understood that those dosages were necessarily given in McNeil's study of ***intermediate grade NHL, a different patient population***.").[3] The Board should reach the same holding here and deny institution.

II. BACKGROUND

A. Technical Overview Of The Invention

The sole claim of the '172 patent is narrowly directed to the treatment of low-grade non-Hodgkin's lymphoma with "CVP therapy to which the patient responds," followed by rituximab maintenance therapy given as four weekly doses of 375 mg/m^2 every six months for two years. Ex. 1001, 22:57-64.[4]

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[3] Emphasis is added to quoted text unless otherwise noted.

[4] CVP, as the Board previously recognized, "is a combination of the drugs cyclophosphamide, vincristine, and prednisone." Ex. 2001, 005.

1. Non-Hodgkin's Lymphomas (NHL)

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. 2002, 004; *see also* Pet. 6 ("NHL is a diverse group of malignant lymphomas…."). "Low-grade lymphoma usually presents as a nodal disease, and is often indolent or slow-growing," whereas "[i]ntermediate and high-grade disease usually presents as a much more aggressive disease…." Ex. 1001, 4:49-52.

As the Board previously found, teachings in the prior art related to intermediate lymphoma, a.k.a., aggressive lymphoma, do not necessarily apply to low-grade lymphoma. *See, e.g.*, Ex. 2001, 018 ("Petitioner does not persuade us that it has explained adequately why an ordinary artisan would have been encouraged to use rituximab maintenance therapy in a ***patient population distinct*** from that described in McNeil."); *Id.*, 021 ("the FDA-approved/recommended weekly rituximab dosage for relapsed or refractory LG-NHL might be the same as the dosage recited in claim 1 does not demonstrate that a skilled artisan would have understood that those dosages were necessarily given in McNeil's study of ***intermediate grade NHL, a different patient population***."). This is because the type of lymphoma is "the major determinant[] for treatment outcome and

prognosis" as the diseases differ "in sensitivity to…chemotherapy." *See* Ex. 2003, 001-2.

Low-grade NHL is a deadly cancer that is "low-grade" in name only. The term "low-grade" in NHL refers to the speed with which the disease progresses, not its severity. At the time of the invention, a diagnosis of LG-NHL meant a very poor prognosis because the disease was (and still is) a chronic, incurable cancer. "Despite a high initial response rate to chemotherapy, this lymphoma demonstrates a relapse pattern." Pet. 7. "Following treatment, subsequent remissions occur at a lower rate with shorter response duration." *Id.* And, unfortunately, "[m]ost patients eventually die from the disease or its complications." *Id*. In contrast, patients with intermediate-grade NHL were frequently cured. *See* Ex. 2003, 002 ("high-grade lymphomas of all stages are generally treated with curative intention, final disease eradication cannot be achieved in low-grade lymphomas"); Ex. 1017, 030 ("Most patients with intermediate- or high-grade lymphomas who achieve a complete remission with therapy may be cured.").

2. Treatment Of Low-Grade NHL And Aggressive NHL

Traditionally, the type of lymphoma from which a patient suffered dictated the chemotherapeutic regimen used. Most chemotherapy regimens used for LG-NHL were not used for intermediate-grade NHL (IG-NHL, also called

aggressive NHL), and vice versa. *Compare* Ex. 1017, 029, Table 111-7 (listing chemotherapy used for low-grade lymphoma) *with id.*, 031, Table 111-8 (listing chemotherapy used for intermediate-grade lymphomas). CHOP chemotherapy[5]—was an exception, as it was used for both. *Id.* Chemotherapy was used to induce remission of the cancer (referred to as "induction" therapy).

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, such as the combination regimen "BCVP," that were successful as induction therapies were not successful as maintenance therapies. *See* Section VI.A.4.a. Similarly, biologic drugs, such as interferon, that had been tried as maintenance therapy were unsuccessful. *Id.* 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. 2004, 008. The result was frequent recurrence of the low-grade lymphoma, *i.e.*, "relapse," after initial responses to chemotherapy.

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[5] CHOP is a chemotherapy regimen consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone.

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, 1:47-50, 5:35-43. Most B-cell lymphomas express CD20, *id.* at 1:27-41.[6] By the priority date, the FDA had approved rituximab as monotherapy to treat relapsed or refractory, low-grade NHL. *Id.*, 1:47-50.

B. Prosecution History

During examination, the Patent Office issued a restriction requirement compelling Patent Owner "to elect a particular form of NHL" because the different types of NHL are patentably distinct. *See* Ex. 2005, 003. The Office also compelled Patent Owner to elect "a specific chemotherapy protocol" because the different chemotherapy regimens are "patentably distinct species." *Id*. Patent Owner elected LG-NHL and CVP therapy. Ex. 2006, 008. Petitioner's present attempt to challenge patentability by equating aggressive NHL with low-grade NHL, and CHOP therapy with CVP therapy, contradicts the Office's correct view

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[6] A known danger of multiple treatments with rituximab, however, was antigen escape, whereby cancerous B cells would develop resistance by losing expression of CD20. *See* Section V.A.3.b. below.

that skilled artisans would viewed these cancers and chemotherapies as significantly different.

C. Previous IPR Proceedings

Boehringer Ingelheim filed an IPR petition in December 2014 against the '172 patent (IPR2015-00418). In that petition, Boehringer raised grounds for invalidity substantially similar to those now argued by Petitioner.

Boehringer argued that the '172 patent claim was anticipated by the "ECOG 1496 protocol" and "Suggested Patient Consent Form" (there presented as a single exhibit). Petitioner now raises the same argument in Grounds 1 and 2 of this proceeding.

Boehringer also argued that the McNeil news article (Ex. 1005), which reported on an ongoing clinical study using rituximab maintenance following CHOP induction therapy in elderly patients with intermediate-grade NHL, in combination with the Rituxan® label and other references, rendered the '172 patent claim obvious. Petitioner now raises a cumulative argument in Ground 4 of this proceeding.

The Board denied institution on all grounds, finding insufficient evidence that the "E1496 Protocol" (which included the "Suggested Patient Consent Form") was a publicly accessible printed publication. Ex. 2001, 008. The Board also found

that the petitioner failed to show that skilled artisans would (1) "modify McNeil's treatment of patients with intermediate grade NHL to instead treat the LG-NHL," (2) "modify McNeil's CHOP treatment to instead use the CVP treatment," (3) apply the FDA-approved rituximab dosage for relapsed disease to the maintenance therapy setting, and (4) believe that alleged success with interferon maintenance therapy indicates that rituximab maintenance therapy would be successful. *Id.*, 021. The Board's decision is further discussed below in the applicable sections of this preliminary response.

III. CLAIM CONSTRUCTION

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

The Board previously construed the term "CVP therapy to which the patient responds, followed by rituximab maintenance therapy" to mean that the patient must have experienced a complete or partial response, as defined by the criteria specified in the specification:

> [W]e construe claim 1 as requiring administration of CVP therapy, to which the patient responds according to the criteria set forth in the '172 patent. See Ex. 1001, 9:14-23 (the '172 patent providing specific criteria for a complete response (CR) and a partial response (PR) and distinguishing such patients from "non-responders"). The

> CVP must be followed at some time by the rituximab maintenance therapy, with no disease relapse occurring between the patient's response to the CVP therapy and the maintenance therapy.

Ex. 2001, 006. Petitioner agrees with this construction. Pet. 25-26.

The cited portion of the '172 patent defines the clinical criteria for complete and partial responses as:

> ***Complete response*** required the regression of all lymph nodes to $<1\times1$ 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, 9:14-23.

Patent owner agrees with petitioner that the Board's prior construction should be adopted. *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.").

B. "chemotherapy consisting of CVP therapy"

Petitioner argues that, despite its "consisting of" transition, Claim 1 "allows additional unrecited method steps to be performed, including the co-administration of other therapies, such as induction rituximab or myoablative [sic] therapy, in addition to CVP, followed by rituximab maintenance therapy." Pet. 26. Because Petitioner's petition does not rely on this comment, the Board need not decide on Petitioner's proposed interpretation of Claim 1.

IV. PETITIONER FAILS TO ESTABLISH THAT THE "E1496 PROTOCOL," "SUGGESTED PATIENT CONSENT FORM," AND "RITUXAN LABEL" ARE PRINTED PUBLICATIONS

As the Board recognized in the prior IPR, "[t]he Federal Circuit has held that 'public accessibility' is 'the touchstone' in determining whether a reference is a printed publication. *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986)." Ex. 2001, 008. "A given reference is 'publicly accessible' upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art[,] exercising reasonable diligence, can locate it." *Id.* (citing *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008)).

A. Petitioner Fails To Establish That Exhibits 1008 ("Suggested Patent Consent Form") And 1009 ("E1496 Protocol") Are Printed Publications

Like the petitioner in the prior IPR, Petitioner here relies on a document it describes as an ECOG clinical trial protocol or "E1496 Protocol" (Ex. 1009) that is not, as the Board previously concluded, a "printed publication." Ex. 2001, 008. Petitioner also separates as an exhibit the "Suggested Patent Consent Form" (Ex. 1008) that is an appendix to Exhibit 1009. And like the petitioner in the prior IPR, Petitioner fails to explain "how or where it obtained the ECOG protocol[]," which includes the "Suggested Patent Consent Form" as an appendix. *See id.*, 010.

Petitioner's printed-publication arguments are the same as those advanced by the prior petitioner. Petitioner asserts that: (1) a skilled artisan allegedly could have, by May 1998 (the "activation date" of the study), learned about the E1496 clinical trial by going to the ECOG website; and (2) the protocols and patient consent forms for these trials allegedly were available, by May 1998, to any interested physician who requested them. Pet. 30-32. Again, neither of these assertions is supported by competent evidence. The Board should reach the same conclusion it did last time.

1. There Is No Evidence That A Person Of Skill Exercising Reasonable Diligence Would Have Located The "E1496 Protocol" And "Suggested Patient Consent Form" Before The Priority Date

Petitioner argues that a POSA could have located the "E1496 Protocol" and "Suggested Patient Consent Form" on the ground "that any interested physician could have learned about the E1496 trial by viewing the list of active protocols on the ECOG website." Pet. 31. Petitioner cites Exhibit 1049, a purported printout of the ECOG webpage from May 19, 1998. The Board should reject Petitioner's argument, even assuming the alleged webpage was publicly available before the priority date.

The same webpage was cited by the petitioner in the prior IPR. There, the Board held that "[a]lthough…the archived ECOG website lists ECOG 1496…among active trials [Ex. 1049]," the webpage was insufficient to establish public accessibility to the protocol for multiple reasons:

> [1] the ECOG protocol listings are not in the form of hyperlinks [*see* Ex. 1049], [2] the full archived website does not otherwise appear to contain the protocols at issue or links to them (*see* [Ex. 2011], generally), [3] the archived website lists the search function as 'not yet available' (*id.* at 107), and [4] the link to the ECOG

> members portion of the website indicates that a password is required for entry (*id.* at 1).

Ex. 2001, 012-13. Petitioner has not addressed any of these shortcomings, and therefore, the Board should again hold that the ECOG website is insufficient to show that either the "E1496 Protocol" or "Suggested Patient Consent Form" were publicly available.

Petitioner asserts that the webpage provides "sufficient detail" to serve as an appropriate index because it included "the protocol number." Pet. 31. This 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 1049 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 1049, it would not lead such a person to seek a copy of the underlying protocol. The clinical study E1496, for example, is described in Exhibit 1049 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, as opposed to, for example,

interferon therapy. *See* Ex. 2007, generally (broadly describing "biologic therapy" as "gene therapy" and "immunotherapy," such as cellular therapy, cytokines and antibodies). Petitioner does not argue otherwise.

Like the prior IPR petitioner, Petitioner has failed to show that a skilled artisan would have reviewed the ECOG website, and then sought and obtained copies of the E1496 protocol and suggested patient consent form on the basis of that website.

Moreover, Petitioner has not even established that the alleged webpage was publicly available before the priority date. Relying on a declaration by Christopher Butler (also Ex. 1049), Petitioner concludes that the ECOG webpage was available online on May 19, 1998. But the Butler declaration only attests to how the Internet Archive "assigns" URLs now, not what it allegedly did back in 1998 when the webpage was allegedly archived. Ex. 1049, 001 (statement in present tense).

Even if the Internet Archive assigned URLs the same way in 1998, this statement would still be insufficient because it was not the Internet Archive's web crawler that captured the ECOG webpage at issue. This important fact was omitted in the Exhibit 1049 printout of the webpage, https://web.archive.org/web/19980519084342/http:/ecog.dfci.harvard.edu/~ecogdba/active_reports/Lymphoma.html. A true copy of the webpage is submitted as

Exhibit 2008. As can be seen in Exhibit 2008 at 1, there is an "About this capture" toggle on the top right of the page. When this toggle is expanded, as shown in Exhibit 2008 at 2, the webpage explains that the capture of the relevant URL was done by an organization called Alexa Crawls, not the Wayback Machine. The Butler declaration does not even purport to address Alexa's web crawlers or archiving practices at any time, much less back in 1998. Nor does it address how or when the pages allegedly archived by Alexa Crawls were donated to the Internet Archive.

2. Dr. Longo's Declaration Does Not Establish That The Protocol And Consent Form Were Publicly Accessible.

Given the lack of any documentary evidence demonstrating public accessibility, Petitioner tries to shore up its argument by offering the testimony of Dr. Walter Longo, a physician at the University of Wisconsin Clinical Cancer Center ("UWCCC") located at the UW Hospital and Clinics, who testifies that UWCCC was a member of ECOG. *See* Pet. 29; Ex. 1002, ¶25. His testimonial evidence fails to establish that Exhibits 1008 and 1009 are printed publications.

Although Dr. Longo states that he generally "received the trial protocols directly from the UWCCC data coordinators," he does not testify that he received either Ex. 1008 or Ex. 1009 in particular, and importantly, does not say whether he

received any such documents before the priority date. *See* Ex. 1002, ¶39. Neither Exhibit 1008 or 1009 was found in the files of the data coordinator of his institution. *See* Ex. 1002, ¶16 and footnotes 1-2 (describing Exhibit 1066 and 1068 as documents found in the coordinator's office, but not saying the same for Exhibits 1008 and 1009).

Indeed, Exhibit 1008, on its face, does not appear to be a copy of an actual consent form distributed to patients. Exhibit 1008, the alleged "E1496 Patient Consent Form," appears to be another document's "Appendix I" that is titled and includes language for a "***Suggested*** Patient Consent Form." Ex. 1008, 001. "Local IRB changes to this document [were] allowed." *Id.* The document also states that "revis[ions]" could be made if "justification" is sent to the ECOG main office. *See id.*

Dr. Longo does not have any firsthand knowledge of how the "E1496 Protocol" and "Suggested Patient Consent Form" allegedly were distributed from ECOG's central office (located in Massachusetts, Ex. 1009, 001) or from any institution affiliated with ECOG other than his own.

And even with respect to his own institution, Dr. Longo cites no documents supporting his assertions that "the E1496 Patient Consent Form and Protocol were freely available to potential patients and interested clinicians without any

confidentiality restrictions as of March 1998" (Pet. 29, citing Ex. 1002, ¶¶49, 52-53, 63), and "UWCCC would routinely disclose the E1496 Protocol to any inquiring physician, so that the physician could be fully informed about the potential risks and benefits of the E1496 trial before referring patients to the institution" (Pet. 31, citing Ex. 1002, ¶57). This uncorroborated testimony should be viewed with skepticism. *Finnigan Corp. v. United State ITC*, 180 F.3d 1354, 1366 (Fed. Cir. June 9, 1999) ("The law has long looked with disfavor upon invalidating patents on the basis of mere testimonial evidence absent other evidence that corroborates that testimony.").

But even if given weight, Dr. Longo's unsupported statements still fall short of establishing that the two exhibits at issue were publicly accessible to skilled artisans.

a. *Insufficient Evidence Of Public Distribution To Skilled Artisans*

Petitioner asserts that Dr. Longo "distributed the consent form to approximately 40 prospective patients, every prospective patient who inquired about the E1496 trial." Pet. 30. But significantly neither petitioner nor Dr. Longo states ***when*** such distribution allegedly occurred.

In particular Dr. Longo does not claim that he distributed the alleged "Suggested Patient Consent Form" to any patients before the August 1999 priority date. Instead, Dr. Longo merely says that he "personally enrolled some of [the] thirteen patients" that "were treated at [his] study site, UW Hospital and Clinics." Ex. 1002, ¶40. Based on the "Protocol Accrual" document (Ex. 1068, 003-4) on which Dr. Longo relies, only one patient at his study site was "On Study" before the priority date, and Dr. Longo does not testify that he personally enrolled that patient. He thus offers no testimony from personal knowledge as to what documents were, or were not, provided to the only patient treated at his institution before the priority date (or, for that matter, to any other person before the priority date). Nor does he offer any testimony regarding whether Exhibit 1008, an "Appendix I" containing a "Suggested Patient Consent Form," was given without modification to any patient before the priority date.

Importantly, even if one patient received the consent form before the priority date, this would not establish the consent form as a printed publication. *See Preemption Devices, Inc. v. Minnesota Mining & Mfg.*, 732 F.2d 903, 906 (Fed. Cir. 1984) (finding that mailing a document to a single recipient does not transform the document into a printed publication where "[t]here is no evidence to show further dissemination by the [recipient] before the critical date").

Moreover, that a patient may have received a copy of a consent form before the priority date does not prove public dissemination to ***skilled artisans***. *See SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (requiring that a reference must be "publicly accessible…[to] persons interested and ordinarily skilled in the subject matter or art."). Dr. Longo's passive assertion that "[i]t was expected that such patients would take the consent form home and discuss the pros and cons of the clinical trial with their own physicians, other oncologists who might provide second opinions, family members, friends, co-workers, and anyone else before deciding whether to enroll," Ex. 1002, ¶49, does not constitute evidence that such discussions ever occurred, much less that Ex. 1008 itself, as opposed to just general information about the study, was "further disseminat[ed]." *Preemption Devices*, 732 F.2d at 906. It is simply speculation to assume otherwise.

b. *Insufficient Evidence Of Public Availability*

Petitioner asserts that "ECOG affiliates would also distribute letters listing all active ECOG trials to any physician requesting such information." Pet. 31. But Dr. Longo does not say that UWCCC ever sent such a letter listing E1496, let alone produce a copy of any such letter. He merely says that "[s]tarting in March 1998, these letters from my institution ***would*** include a description of the E1496

Protocol." Ex. 1002, ¶56. That is subjunctive speculation. So is his statement that UWCCC "***would*** routinely disclose the E1496 Protocol to any inquiring physician." *Id.*, ¶57. Nowhere does Dr. Longo state that any non-ECOG physician inquired of UWCCC about the "E1496 Protocol" nor that anyone at the UWCCC, including himself, actually disclosed the "E1496 Protocol" to any such physician.[7] This is fatal to Petitioner's argument.

In *Norian Corp. v. Stryker Corp.*, the Federal Circuit agreed that a purported prior-art reference "did not meet the criteria of § 102(b) because it was available

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[7] Petitioner has not argued that alleged distribution of the E1496 protocol to ECOG physicians could render it a printed publication. And indeed, such non-public distribution would be insufficient. *Northern Telecom.* v. *Datapoint Corp.*, 908 F.2d 931, 936-37 (Fed. Cir. 1990) (holding that even if a reference could be located by particular individuals, it is not a printed publication unless it is "generally available" to the public). 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.

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). 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.*

B. Petitioner Fails To Offer Any Evidence That Ex. 1004 ("The Rituxan® Label") Is A Printed Publication

To prove that a document is a printed publication, it is not enough merely to assert that the document is an FDA-approved label that was publicly available by a certain date; yet, this is ***all*** Petitioner does in its petition for Exhibit 1004.

The Board's decision in *Mylan Pharms. v. Boehringer Ingelheim Int'l GmbH*, IPR2016-01566, Paper 15 (Feb. 3, 2017) is on point. There, the "Petitioner contend[ed] that the Glucophage® Label qualifies as prior art under 35 U.S.C. §102(b) because it was approved and published by the FDA for treating type 2 diabetes in February 2001." *Id.* at 10. In its decision denying institution, the Board held that the purported label itself, without more, was insufficient to show it was a publicly accessible printed publication. *Id.* at 11. So too here. Exhibit 1004 contains none of the hallmarks of a document published or disseminated prior to the priority date. Petitioner, in fact, never explains how it came into possession of the document it submits as Exhibit 1004.

Even assuming that Exhibit 1004 contains information consistent with a Rituxan® label, Petitioner has offered ***no*** evidence to show that Exhibit 1004 is a copy of an actual document publicly disseminated before the priority date. Indeed, the document actually suggests that it was not a copy of an actual label that was

disseminated with vials of Rituxan® or otherwise distributed. Exhibit 1004 bears what appears to be handwriting at the top of the document partially spelling "***Rit***uximab" in vertical orientation. Ex. 1004, 001. It is highly unlikely that a document with half the product name written in by hand was distributed with Rituxan® drug packages.

That Exhibit 1004 bears a copyright date of 1997 says nothing about whether it was ever actually publicly accessible. Indeed, the Federal Circuit has held that even an official certificate of registration from the Copyright Office does not establish a document as a printed publication. *In re Lister*, 583 F.3d 1307, 1312-13, 1317 (Fed. Cir. 2009).

Simply put, petitioners assertion that Ex. 1004 "was made publicly available in November 1997 when Rituxan was approved and is therefore §102(b) prior art," Pet. 34, is a conclusion bereft of supporting evidence.

V. PETITIONER FAILS TO ESTABLISH THAT THE "E1496 PROTOCOL" AND "SUGGESTED PATIENT CONSENT FORM" ANTICIPATE THE CLAIMS (GROUNDS 1 AND 2)

The "E1496 Protocol" and "Suggested Patient Consent Form" are not printed publications, as discussed in Section IV.A, and therefore are not documents on which an IPR may be instituted. *See Teva Pharms. Inc. v. Indivior UK Ltd.*, IPR2016-00280, Paper No. 23 at 8 (June 10, 2016) (a Ground cannot be considered

for institution if Petitioner fails to "provide[] a sufficient threshold showing that the [cited references] constitute prior art").

Even assuming they were, neither would anticipate Claim 1 because neither reference discloses the limitation—"CVP therapy to which the patient responds, followed by rituximab maintenance therapy"—as previously (and properly) construed by the Board. *See* Section III.A.

Petitioner argues that this limitation is met because the words "regresses," "had not progressed," and "maintenance" appear in the references. Pet. 38-41 (claim charts for Grounds 1 and 2). Critically, however, Petitioner fails to match those words or phrases to "the [response] criteria set forth in the '172 patent." Ex. 2001, 006. As the Board previously held, to meet the claim limitation, the patient must:

> respond[] according to the criteria set forth in the '172 patent. See Ex. 1001, 9:14-23 (the '172 patent providing specific criteria for a complete response (CR) and a partial response (PR) and distinguishing such patients from 'non-responders') following CVP and before the administration of rituximab maintenance therapy.

Id., 006. In turn, the "criteria set forth in the '172 patent" expressly define the clinical criteria for complete and partial responses as:

> ***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.
>
> Patients who did not achieve a CR or PR were considered non-responders, even if a net decrease (>50%) of measurable disease was observed.

Ex. 1001, 9:14-23. As recognized by the Board, the '172 patent claim requires either a complete or partial response, as defined in the specification, following CVP induction and before administration of rituximab maintenance therapy.

The disclosure of the "Suggested Patient Consent Form" (Ex. 1008) does not match the clinical response criteria required by the '172 patent claim. For example, according to the consent form, even patients who do not achieve a complete or

partial response nevertheless also receive rituximab maintenance therapy. Specifically, the consent form discloses that patients whose disease remains the same or regresses on induction chemotherapy would receive rituximab therapy. *See* Ex. 1008, 001 (explaining that rituximab maintenance would be administered "[i]f your tumor ***remains the same or regresses***"). This is inconsistent with the claims which are limited to only those patients who active a complete or partial response.

To the extent Petitioner is asserting that "regresses" suggests a complete or partial response, there is no support for that in the "Suggested Patient Consent Form" itself or in any other part of the record. Moreover, a skilled artisan would have presumed from the "Suggested Patient Consent Form" that patients whose disease "regresses" refers to an improvement insufficient to meet the clinical criteria of partial or complete response as set forth in the '172 patent. This is because the document discloses that even patients those whose disease does not regress at all, *i.e.*, if the "tumor remains the same," would still receive rituximab maintenance. Nothing in the "Suggested Patient Consent Form" teaches administration to those who have a complete or partial response under the express criteria defined by the patent.

Similarly, the "E1496 Protocol" (Ex. 1009) does not require either a complete or partial response before rituximab maintenance therapy is administered.

Instead, patients whose disease had "***not progressed***," regardless of whether the criteria for partial or complete response was met, on induction chemotherapy would receive rituximab therapy. *See* Ex. 1009, 006 ("All patients who have not progressed on induction chemotherapy will be randomized to either maintenance therapy with chimeric anti-CD20 antibody or observation.").

Petitioner's attempt to recast Exhibits 1008 and 1009 to align with the '172 claims is inconsistent with the "E1496 Protocol" itself. The protocol sets its own criteria for determining a complete or partial response (in sections not cited by Petitioner or its expert), and these criteria do ***not*** match the criteria required by the '172 patent. Below are some of the differences (*compare* Ex. 1001, 9:14-23 *with* Ex. 1009, 015):

- Criteria for a ***complete response***: (1) The claim limitation requires measures "on two occasions at least 28 days apart" whereas the Protocol is silent on multiple measurements; (2) The claim limitation requires CT scans of the "neck, chest abdomen, and pelvic" whereas the Protocol requires measurements of "all palpable and x-ray demonstrable disease"; (3) The claim limitation requires "resolution of all symptoms and signs of lymphoma" whereas the Protocol is silent on symptoms and signs; (4) The claim limitation is silent on

failure to enlarge of lymph node whereas the Protocol requires that "[l]ymph nodes of larger size must be documents to be free of tumor on biopsy, or have failed to enlarge over 3 months off-therapy."

- Criteria for a ***partial response***: (1) The claim limitation requires "without any evidence of progressive disease " whereas the Protocol appears to allow at least some progressive disease, e.g., appearance of a new lesion; (2) The claim limitation does not place additional requirements for liver indicator lesions whereas the Protocol requires that certain measures be achieved if "the liver is an indicator lesion;" (3) The claim limitation does not place additional requirements for spleen size whereas the Protocol requires that the spleen must "return to normal size."

Even assuming some overlap between the criteria for complete and partial response in the '172 patent claim and the disclosures of the protocol and consent form, that is insufficient for anticipation, which requires "strict identity." *Trintec Indus., Inc. v. Top–U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002); *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply*, 45 F.3d 1550, 1554 (Fed. Cir. 1995) ("Anticipation requires identity of the claimed process and a process of

the prior art;…the claimed invention, as described in appropriately construed claims, must be the same as that of the reference, in order to anticipate.").

Neither Petitioner nor its expert explains how skilled artisans could understand either the protocol or suggested patient consent form to disclose each and every claim limitation given the differences between what is disclosed and what is claimed. Petitioner has failed to meet its burden of proving anticipation. *See Apple Inc. v. Smartflash LLC*, CBM2014-00105, Paper 9 at 14 (Sept. 30, 2014) (denying institution because "Petitioner does not provide adequate argument or explanation as to why [the prior art disclosure] satisfies the claimed [limitation].").

VI. PETITIONER FAILS TO ESTABLISH THAT THE COMBINATIONS OF REFERENCES IN GROUNDS 3 AND 4 RENDER THE CLAIM OBVIOUS

To prove obviousness, Petitioner 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).

A. Ground 3: Grossbard (Ex. 1010) And The Rituxan Label (Ex. 1004)

As a threshold matter, this Ground fails because Petitioner has failed to show that Ex. 1004, purportedly a Rituxan® label, is a printed publication for reasons discussed in Section IV.B. *See Teva Pharms. Inc. v. Indivior UK Ltd.*, IPR2016-00280, Paper No. 23 at 8 (June 10, 2016) (a Ground cannot be considered for institution if Petitioner fails to "provide[] a sufficient threshold showing that the [cited references] constitute prior art").

The other reference in this Ground, Grossbard, is a two-page review article that provides short descriptions of several ongoing clinical trials testing rituximab in various hematological cancers, including LG-NHL, aggressive NHL, and chronic lymphocytic leukemia. Even though the article's author, Dr. Michael Grossbard, was the petitioner's expert in the prior IPR, neither Dr. Grossbard nor the last petitioner thought this reference was significant enough to cite in its Grounds or even as a background reference. This is because the article's discussion of LG-NHL and rituximab maintenance is so brief and lacking in detail that it fails to evidence any motivation to, or expectation of success for, practicing the claims

of the '172 patent.[8] In fact, as discussed below, it taught the opposite—that there were significant "stumbling blocks" and uncertainties with rituximab dosing.

1. Grossbard Does Not Disclose Any Dosing Regimen For Using Rituximab Maintenance In Low-Grade Lymphoma Following CVP Chemotherapy

The only disclosure of using rituximab maintenance therapy in LG-NHL is found in a single paragraph of Grossbard describing two ongoing clinical trials:

> The value of rituximab maintenance therapy in low-grade lymphoma is the subject of two other cooperative group trials. The Eastern Cooperative Oncology Group (ECOG) is conducting a phase III trial of cyclophosphamide and fludarabine (Fludara) vs CVP (cyclophosphamide, vincristine, and prednisone), followed by rituximab or observation. The Southwest Oncology Group (SWOG) is performing a phase II trial of CHOP followed by rituximab, with special attention to measurement of minimal residual disease.

Ex. 1010, 011.

In one study, CHOP chemotherapy was used as induction therapy. In the other study, patients were assigned FC[9] or CVP as induction therapy. There was no

[8] This article was submitted in an information disclosure statement during prosecution of the '172 patent. Ex. 2028, 020 (reference index D270).

disclosure of what dosing regimen of rituximab was used as maintenance therapy in either study. *Id*.

A separate paragraph of the Grossbard article describes a clinical trial, run by Cancer and Leukemia Group B (CALGB), in "elderly patients with aggressive non-Hodgkin's lymphoma." Ex. 1010, 011. These patients received CHOP chemotherapy for induction, and rituximab maintenance therapy was given as "four weekly doses of rituximab every 6 months for 2 years." *Id*. This CALGB study is the same clinical study that is disclosed by the McNeil article (Ground 4), which was considered and found by the Board in the prior IPR not to render obvious the '172 patent claim. *See* Section VI.B.

Petitioner's main argument is that skilled artisans would have used the rituximab dosing regimen from the CALGB study, which treated elderly patients with aggressive NHL following CHOP induction chemotherapy, in the different patient population (patients with low-grade NHL and an unknown age range) following the different induction chemotherapy (CVP) required by the '172 patent claim. *See* Pet. 45.

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[9] FC is a chemotherapy regimen consisting of fludarabine and cyclophosphamide.

But neither Petitioner nor its expert provides any underlying scientific or clinical rationale why skilled artisans would use the same rituximab dosing regimen despite such differences in patient population and induction chemotherapy regimens. Instead, Petitioner appears to rely solely on the fact that the description of one clinical trial is "adjacent" to each other in the article. *See* Pet. 47. This type of conclusory argument is improper as a matter of law. As the Board has previously held, "[unpatentability] on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." Ex. 2001, 018 (citing *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007)). Proximity on the printed page is not a reason to combine under *KSR* and its progeny.

Petitioner's conclusory assumption entirely ignores the Board's prior holding that skilled artisans would understand aggressive lymphoma and low-grade lymphoma as different diseases that should be treated differently. Disclosures related to intermediate or high-grade lymphomas do not necessarily apply to low-grade lymphoma, or vice versa. *See* Ex. 2001, 018 ("Petitioner does not persuade us that it has explained adequately why an ordinary artisan would have been encouraged to use rituximab maintenance therapy in a ***patient population distinct***

from that described in McNeil."); *Id.*, 21 ("[T]he FDA-approved/recommended weekly rituximab dosage for relapsed or refractory LG-NHL might be the same as the dosage recited in claim 1 does not demonstrate that a skilled artisan would have understood that those dosages were necessarily given in McNeil's study of ***intermediate grade NHL, a different patient population***."). This is because skilled artisans knew that aggressive NHL and low-grade NHL responded differently to chemotherapy. *See, e.g.*, Ex. 2009, 001 ("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. 2003, 001 ("Non-Hodgkin's lymphomas…differ…in sensitivity to currently available chemotherapy…."). As a result, aggressive NHL and low-grade NHL were most often treated with different chemotherapy regimens. *Compare* Ex. 1017, 029, Table 111-7 *with id.*, 031, Table 111-8.

A skilled artisan knew, for example, that even with an initial response to chemotherapy, relapses occurred sooner but were exceedingly less common with aggressive NHL than with low-grade NHL. *See* Ex. 2009, 001 (finding that "[p]atients with diffuse histiocytic lymphoma [*i.e.*, aggressive lymphoma] demonstrated the highest rate of relapse during the first year of followup, but late recurrence was uncommon. In contrast, the combined nodular histologic groups

[*i.e.*, low-grade lymphoma]...demonstrated a pattern of continued relapse from remission over a 6-year period of followup").

Most patients with aggressive NHL are cured with chemotherapy and therefore do not relapse. *See, e.g.,* Ex. 1017, 030 ("Most patients with intermediate- or high-grade lymphomas who achieve a complete remission with therapy may be cured."); Ex. 2010, 001 (finding that 76% of "patients with diffuse 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 low-grade NHL continuously relapse until succumbing to the disease. *See, e.g.*, Ex. 2003, 002 ("[F]inal disease eradication cannot be achieved in low-grade lymphomas…."); Ex. 2027, 001-2 ("Relapse [] is the rule" for low-grade lymphoma.); Ex. 2002, 004 ("[R]elapse rate remains high" for "low-grade lymphoma.").

The Board previously recognized, and the record shows, that aggressive and low-grade NHL are materially different in disease severity, relapse rate, remission, prognosis, and therapies used to treat.

Petitioner ignores all of this. It fails to provide a credible rationale why a skilled artisan would use a rituximab maintenance regimen for aggressive NHL in a materially different cancer, low-grade NHL—which has different response and relapse rates. The Federal Circuit faced a similar situation in *Eli Lilly & Co. v.*

Teva Pharm. USA, Inc., 619 F.3d 1329 (Fed. Cir. 2010). 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. The Federal Circuit considered a similar argument again in *American Hospital Supply Corp. v. Travenol Labs., Inc.*, 745 F.2d 1 (Fed. Cir. 1984). In *American Hospital* 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.* So too here.

Petitioner also fails to consider that the patient population in the CALGB study was distinct because it enrolled only elderly patients. Elderly patients were known to respond "markedly less successful[ly]" to therapy, and experience an overall "poorer survival" rate. Ex. 1005, 003. Elderly patients were also more susceptible to the toxicities associated with therapy, *id.* ("CHOP...[and] some other chemotherapy regimens [is known to be] more toxic in this age group."), and as a result, usually were treated with fewer cycle of therapy than younger patients. *Id.*

Elderly patients who respond to therapy also "have a higher relapse rate" than younger patients for unknown reasons. *Id.*, 004. But neither Petitioner nor its expert provides any underlying scientific or clinical rationale why skilled artisans would use the same rituximab dosing regimen from the CALGB study despite differences in lymphoma type and patient population age.

To sum up, the '172 patent claims a method for treating patients with low-grade NHL, a type of lymphoma that is not curable and is characterized by constant relapse. Grossbard discloses a rituximab dosing regimen for a different set of patients, elderly patients with aggressive NHL (a curable disease). These are different diseases in different patient populations understood to require different treatments.

Petitioner's conclusory assumption that the same rituximab dosing regimen would be used across the different clinical trials described in Grossbard, *see* Pet. 47, also ignores the fact that different induction chemotherapies were used in these studies (CHOP was used for elderly patients with aggressive lymphoma, while FC or CVP were used for patients with low-grade lymphoma). Neither Petitioner nor its expert offer any analysis concerning how the difference in chemotherapy would impact what dosing regimen for rituximab should be given. This is especially troublesome considering that rituximab was known to be

synergistic with doxorubicin, which is a component of CHOP but not of FC or CVP. *See* Section VI.B.2.

Ground 3 therefore fails because Petitioner provides no underlying rationale for using the same rituximab dosing regimen being tested in elderly patients with aggressive lymphoma in patients with low-grade lymphoma; nor does it establish any reasonable expectation of success for doing so.

2. Grossbard And The Rituxan Label Do Not Teach Weekly Infusions Of 375 mg/m^2 As A Maintenance Dose

Even assuming that skilled artisans would use the same maintenance regimen from the CALGB study in a different patient population and with different induction chemotherapy, the Grossbard article still fails to disclose the rituximab maintenance dose required by the '172 patent claim: ***375 mg/m^2***. Nowhere in Grossbard is there any disclosure of what dose of rituximab should be given as maintenance therapy.

As recognized in the Grossbard article itself, dosing monoclonal antibodies such as rituximab was a "stumbling block[]" for skilled artisans. Ex. 1010, 010 ("Optimal dosing and adequate tissue penetration represent further stumbling blocks to effective serotherapy….Thus, the best dose and schedule of rituximab remain to be established."). Grossbard also describes that in the non-maintenance

setting, different doses of rituximab had been tried, suggesting "the best dose and schedule of rituximab remain[ed] to be established" even for non-maintenance. Ex. 1010, 010.

Tellingly, even three years after the priority date, Dr. Grossbard wrote that "[f]urther study is needed to establish treatment schedules [for rituximab], such as maintenance therapy after remission induction." Ex. 2026, 005. This statement by Dr. Grossbard belies the assertion that a person of ordinary skill would have found it obvious to give rituximab at 375 mg/m^2 weekly for maintenance at the time of the invention.

With little analysis, Petitioner cites Ex. 1004 (the "1997 Rituxan Label") in an effort to fill the hole in Grossbard, arguing that "the 1997 Rituxan label teaches the administration of rituximab in four weekly doses of 375 mg/m^2." *See* Pet. 3; Ex. 1003, ¶91. But even if Petitioner had shown that Ex. 1004 was a prior art printed publication, the label only recommended the regimen of four weekly doses of 375 mg/m^2 for treatment of ***relapsed or refractory*** low-grade NHL, not as maintenance therapy. Petitioner 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.

As the Board previously held, "relapsed patients…are beyond the scope of claim 1," Ex. 2001, 018, and the fact the weekly infusion amount for relapse disease is 375 mg/m^2 "does not demonstrate that a skilled artisan would have understood that those dosages were necessarily given" in a maintenance setting. *See id.*, 021 ("[T]hat the FDA-approved/recommended weekly rituximab dosage for relapsed or refractory LG-NHL might be the same as the dosage recited in claim 1 does not demonstrate that a skilled artisan would have understood that those dosages were necessarily given in [a clinical maintenance] study of intermediate grade NHL, a different patient population.").

In fact, the data presented in Celltrion's own reference 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 setting. In such a setting, Ex. 1004 suggests use of a ***lower*** dose. The pharmacokinetic section of Ex. 1004 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. 1004, 001 ("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."). Lower serum levels were due to

a phenomenon known as tumor sink, whereby tumor cells would sequester the rituximab and reduce its effective serum concentration.

Indeed, Petitioner'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. 44 ("A POSA would understand that maintenance therapy is given only after successful induction chemotherapy, after a patient has experienced a complete or partial response and is in remission.").

Given the description in Ex. 1004 of the pharmacokinetic profile of rituximab, a skilled artisan would not have used the relapsed doses of 375 mg/m^2 for maintenance therapy, where the patients had responded to, rather than relapsed from, prior chemotherapy. If anything, a skilled artisan would have used less rituximab as maintenance therapy by decreasing the amount (mg/m^2) given in each weekly administration.

In the face of the data in Ex. 1004 suggesting that the dose for relapsed disease would not be appropriate in the maintenance setting, Celltion cites only the unsupported opinion of Dr. Lossos to argue otherwise. *See* Pet. 47, *citing* Ex. 1003, ¶91, 94. Dr. Lossos offers no explanation, and cites no evidence, for his assertion that the weekly 375 mg/m^2 dosing would be used or would be expected to succeed. The Board should 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.").

Elsewhere, Petitioner argues, "it was well-appreciated that the approved dosing schedule of rituximab of 375 mg/m^2 weekly for four weeks caused the depletion of normal and malignant B-cells for six to nine months. (Ex. 1003, ¶67; Ex. 1042 at 003, 006.)." Pet. 18-19. But the goal of rituximab maintenance therapy was not to "cause[] the depletion of normal and malignant B-cells," which would already have been relatively low or even undetectable. The goal of rituximab maintenance therapy was to ***prevent an increase*** in the number of malignant B-cells, *i.e.*, maintain a response and prevent relapse.

Petitioner's conclusion that it would have been obvious to use the relapse dose for maintenance instead, without any analysis or any discussion of the differences between the treatment of relapsed patients and responsive patients, 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).

3. Grossbard And The "Rituxan Label" Do Not Disclose Or Suggest The Specific Complete And Partial Responses Required By The Claim

As discussed in Section III.A, the Board construed Claim 1 as requiring a patient response prior to rituximab maintenance therapy according to "specific criteria for a complete response (CR) and a partial response (PR)." Ex. 2001, 006, citing Ex. 1001, 9:14-23 (describing specific clinical outcomes for CR and PR). Petitioner has failed to establish that the art disclosed or suggested this limitation.

4. Petitioner Fails To Establish A Reasonable Expectation Of Success For Using The Disclosed Rituximab Maintenance Regimen

Grossbard also fails to provide any support for Petitioner's assertion that there was a reasonable expectation of success for using rituximab as maintenance therapy for low-grade lymphoma. First, Grossbard reports only that clinical trials were being conducted to "explor[e] the value of rituximab maintenance therapy…in low-grade lymphoma"; it provides no results or data of any kind. Ex. 1010, 011. On the contrary, the article explains that whether rituximab's "activity is augmented in the minimal disease setting" was unknown. *Id.*, 010. Petitioner never explains, much less offers evidence, why a skilled artisan

reviewing Grossbard would have any reasonable basis to believe rituximab maintenance therapy would work. This is especially problematic when the article itself notes that "[a]lthough the concept of MoAb therapy is simple, ***a host of unforeseen difficulties*** hindered the realization of clinical benefit from this therapeutic approach." *Id.* The article further acknowledges that the optimal rituximab dose is unknown even for non-maintenance use and a "stumbling block[] to effective" therapy. *Id.* ("Optimal dosing and adequate tissue penetration represent further stumbling blocks to effective serotherapy [of rituximab].").

a. *No Successful Maintenance Therapy Had Been Established In The Prior Art*

At the time of the invention, despite the efforts of many, no maintenance therapy had been shown to effectively maintain remission and prevent relapse of low-grade NHL. That is why "[m]aintenance therapy [was] ***rarely employed*** in non-Hodgkin's lymphoma once a clinical complete response has been obtained." Ex. 2004, 008.

Petitioner presents no evidence of genuine success with either biologics maintenance or chemotherapy maintenance. Petitioner cites Exhibit 1025 as purporting to show that "[s]ome trials showed that these maintenance therapies prolonged remission and improved overall survival." Pet. 17. But Exhibit 1025 is a

review article, not a clinical study. And the article summarized the clinical experience with maintenance chemotherapy as not altering "the pattern of continuous relapse and the duration of median survival." *Id.*, 003. The article notes that any "benefit in time to failure was offset by time on treatment." *Id.* The article did not, contrary to Petitioner's description, report that chemotherapy maintenance "improved overall survival." Pet. 17.

Indeed, Petitioner's own reference concluded that chemotherapy and biologics used for induction had "no significant effect on overall survival" when used as "[m]aintenance therapy after complete remission." *See* Ex. 1007, 005. As an example, maintenance therapy with the chemotherapy regimen BCVP "did not translate into any appreciable survival advantage." Ex. 2012, 004. Using chemotherapy as maintenance was also associated with "increased toxicity, reduced patient well-being, and increased risk of secondary malignancies." Ex. 2013, 001; Ex. 1025, 003 (summarizing the clinical experience with maintenance chemotherapy as not altering "the pattern of continuous relapse and the duration of median survival").

Similarly, biologic drugs that had been tried as maintenance therapy—including BCG (traditionally a tuberculosis vaccine) and interferon (a cytokine also used to treat infections)—likewise were unsuccessful. *See, e.g.*, Ex. 2014, 003

(Explaining that because of poor outcomes in clinical trials, "the weight of evidence does not provide a compelling reason to recommend further study [of BCG] . . . as maintenance therapy."). Many prior art studies had found interferon (IFN) to be unsuccessful as maintenance therapy in LG-NHL. *See, e.g.*, Ex. 2015, 002 ("To date, no additional benefit has been seen from the administration of IFN for maintenance."); Ex. 2016, 003 ("We conclude that alpha-interferon consolidation after intensive induction chemotherapy does not prolong progression-free survival or overall survival in patients with low-grade malignant lymphoma"); Ex. 2017, 003 ("The use of IFNa as maintenance may have a slight effect on response duration, but does not have an impact on survival."); Ex. 2018, 001 ("During maintenance therapy with interferon alfa-2b, no significant differences in the occurrence of relapse have yet been seen compared to patients on no maintenance therapy."); Ex. 2019, 007 (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."). Contrary to Petitioner's assertion, skilled artisans did not view interferon maintenance therapy as having showed success, which is why, "[m]aintenance therapy [was] rarely employed in non-Hodgkin's lymphoma once a clinical complete response has been obtained." Ex. 2004, 008.

Even assuming that one or two clinical studies showed a potential benefit of interferon or chemotherapy maintenance therapy, neither Petitioner nor its expert explain how skilled artisans would have weighed those results against the multiple failures, let alone how the results would have led to a reasonable expectation of success using rituximab in maintenance therapy.

As the Board held in the prior IPR, a POSA would not have thought that allegedly successful interferon maintenance therapy indicated that rituximab maintenance therapy would be successful:

> As Patent Owner argues (Prelim. Resp. 44), interferons were thought to boost the patient's immune system, including stimulating B-cells….In contrast, rituximab inhibits the immune system by killing B-cells. See Ex. 1008, 1 (Rituximab administration "resulted in a rapid and sustained depletion of circulating and tissue-based B-cells."). Given the significant differences in their biological activities, Petitioner does not persuade us, on this record, that interferon and rituximab would have been considered functionally equivalent biologics, such that an ordinary artisan would have been prompted to substitute one for the other.

Ex. 2001, 020; *see also id.*, 024 and 026-27 (accord).

The many failures of maintenance therapy in low-grade NHL test in the art underscore the unpredictability in this field, and rebut Petitioner's contention that skilled artisans would have had a reasonable expectation of success in developing a successful rituximab 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 in light of this background of other failures, short review articles, such as Grossbard, announcing the start of another study cannot support an expectation of success.

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

Moreover, Petitioner's petition fails to address another reason why a skilled artisan would have been skeptical about successfully using rituximab as maintenance therapy in low-grade NHL: reported antigen escape with repeated rituximab treatments in low-grade NHL. Ex. 2020, 002. Antigen escape is a phenomenon whereby repeated use of rituximab causes cancerous cells to lose expression of CD20 thereby becoming treatment resistant. 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*. Because of

this risk of antigen escape, skilled artisans would have been skeptical about the success of rituximab as maintenance therapy.

In fact, before the effective filing date of the ʾ172 patent, the author of the primary reference, Dr. Grossbard, published his own 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. 2021, 3696; *see also id*., 3704 (same). Such uncertainty in the art precludes finding a reasonable expectation of success.

Because maintenance is a form of recurrent treatment, this risk of antigen escape would have caused a skilled artisan to be skeptical about the prospects of success of rituximab as maintenance therapy.

c. *Petitioner Fails To Establish A Reasonable Expectation Of Success For Using Rituximab As Maintenance Therapy In Low-Grade Lymphoma.*

A careful look at Petitioner's Petition reveals that it has offered nothing but conclusory statements on the likelihood of ***successfully*** using rituximab as maintenance therapy in low-grade lymphoma.

Petitioner simply writes, at multiple points in its petition, that a "POSA would have had a reasonable expectation that rituximab would be safe and efficacious as maintenance therapy." Pet. 58; *see also id*., 48-49 ("A POSA would

have expected rituximab maintenance therapy to be safe and efficacious based on the previous trials of rituximab"); *id.*, 56 ("[A] POSA reading McNeil would have reasonably expected that rituximab maintenance therapy following standard chemotherapy would be safe and efficacious.").

Petitioner attempts to explain why rituximab would have been expected to be ***safe***. *See, e.g.*, Pet. 12-13, 48-49. But Petitioner's petition fails to address why skilled artisans allegedly would have had a reasonable expectation of ***efficacy*** for rituximab maintenance therapy, at the claimed dose, in low-grade lymphoma after exhibiting a partial or complete response to CVP induction therapy. This is especially problematic because, as discussed in Section VI.A.4.a, no maintenance therapy had demonstrated success as of the priority date. Petitioner's conclusory statements are insufficient.

At one point, Petitioner cites McNeil (Ex. 1005) and Grossbard (Ex. 1010) for the proposition that "[a]s early as February 1998, publications ***described promising results*** from studies that used rituximab maintenance therapy following chemotherapy. (Ex. 1005, 003; Ex. 1010, 011.)" Pet. at 2. That is demonstrably untrue. Neither McNeil (Ex. 1005) nor Grossbard (Ex. 1010) describes any results whatsoever. Both merely allude to ongoing clinical trials.

As the Board held in the previous IPR, the fact that prior art "suggest that rituximab maintenance therapy might warrant further study" does not mean that skilled artisans would have viewed that art "as encouraging rituximab maintenance therapy in LG-NHL." Ex. 2001, 024; *see also id.*, 026-27 (same).

B. Ground 4: McNeil (Ex. 1005), Bishop (Ex. 1006), Dana (Ex. 1007), and "the Rituxan Label" (Ex. 1004)

As a threshold matter, this Ground fails because Petitioner has failed to show that Ex. 1004 is a printed publication for reasons discussed in Section IV.B. *See Teva Pharms. Inc. v. Indivior UK Ltd.*, IPR2016-00280, Paper No. 23 at 8 (June 10, 2016).

The primary references in this Ground are McNeil and "the Rituxan label," both of which the Board already considered and found unpersuasive in the prior IPR proceeding. None of Petitioner's arguments would lead to a different holding now.

The Board recognized that McNeil materially differed from the limitations of Claim 1 in "at least three respects":

> McNeil differs from claim 1 of the '172 patent in at least three respects: (1) McNeil treats patients with intermediate grade NHL (IG-NHL), rather than the low-grade NHL (LG-NHL) treated in claim 1, (2) McNeil

> does not teach rituximab maintenance therapy following CVP induction therapy as required by claim 1, but instead teaches CHOP induction therapy, and (3) McNeil is silent as to the dosing for maintenance therapy and, therefore, does not teach claim 1's rituximab maintenance regimen of four weekly doses of 375 mg/m^2.

Ex. 2001, 015-16.

Petitioner argues that "new" references not raised in the prior IPR, Bishop and Dana, teach that CVP is less toxic than CHOP and therefore render obvious the CVP induction therapy required by the '172 patent claim. This argument is cumulative of one already made by the previous petitioner and rejected by the Board. *See* Ex. 2001, 017 (finding it was not obvious to substitute CVP for the CHOP taught by McNeil despite the fact that, "Petitioner cites the Hiddemann reference, to explain that an ordinary artisan would have been motivated to substitute CVP for CHOP because CVP had lower toxicity and was therefore a standard induction therapy for LG-NHL").

Nothing offered by Petitioner in these proceedings should change the Board's prior analysis and holding. Indeed, Petitioner's "new" references do nothing to address the Board's prior finding that McNeil fails to disclose use of

rituximab maintenance for low-grade lymphoma and does not teach a maintenance regimen of four weekly doses of 375 mg/m^2.

1. McNeil (Ex. 1005) Does Not Disclose Rituximab Maintenance For Low-Grade Lymphoma

As the Board previously recognized, "McNeil describes a clinical trial for elderly patients with intermediate-grade non-Hodgkin's lymphoma (IG-NHL) in which patients who responded to CHOP chemotherapy, 'the standard chemotherapy for this form of NHL,' were 'assigned to receive [a] maintenance regimen—Rituxan every 6 months for 2 years—or observation.'" Ex. 2001, 015. This is the same CALGB clinical study disclosed by the Grossbard article, discussed in Ground 3, and McNeil discloses no more about the study than Grossbard does.[10] *See* Section VI.A.

In the prior IPR, the Board rejected an argument that "an ordinary artisan would have been prompted to modify McNeil's treatment of patients with intermediate grade NHL to instead treat the LG-NHL required by claim 1 of the

[10] The McNeil article states that this study in elderly patients with aggressive NHL was organized by ECOG, whereas the Grossbard article refers to it as a CALGB study. In fact, both cooperative groups were involved in running the study. *See* Ex. 2022, 001.

'172 patent." Ex. 2001, 021; *see also id.*, 014-15 (rejecting the argument that "it would have been obvious to those of ordinary skill to use the protocol described in McNeil to treat LG-NHL"). As explained in Section VI.A.1, this is because aggressive-grade lymphoma and low-grade lymphoma are disparate diseases that are treated with different agents and dosing regimens, and respond differently to treatment.

Like Grossbard, McNeil reported only on the commencement of the study; it provided no results or data of any kind. It simply speculated that rituximab maintenance in that particular setting—following CHOP-based induction in patients with IG-NHL, *i.e.*, aggressive NHL—would be a "***possible*** improvement." Ex. 1005, 003. Petitioner never explains why, much less offers evidence that, a POSA reviewing McNeil would have had 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 (and Grossbard) would ultimately show that the proposed rituximab maintenance therapy regimen was ***not*** effective after R-CHOP induction therapy in IG-NHL. *See* Ex. 2022, 001 ("After R-CHOP, no benefit was provided by MR [maintenance rituximab].").

This failure to show efficacy with rituximab maintenance therapy in IG-NHL underscores the unpredictability in this field. As discussed in Section VI.A.4.a, the field was replete with other maintenance-therapy failures, rebutting Petitioner's contention that a skilled artisan would have had a reasonable expectation of success in developing an efficacious maintenance treatment.

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: low-grade NHL. *See Eli Lilly*, 619 F.3d at 1338 (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"). Even if McNeil showed that IG-NHL patients were responsive to the disclosed maintenance therapy, a skilled artisan would have recognized that any responsiveness in IG-NHL could not presumptively be applied to LG-NHL.

As discussed in Section VI.A.1, the CALGB study disclosed by McNeil not only treated a different patient population, but also used a different induction chemotherapy, than the claim limitation. Whatever alleged suggestion of success

Petitioner 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. Petitioner simply resorts to unsubstantiated speculation, and McNeil cannot support the weight of Petitioner's claims. This is precisely what the Board found in the last IPR.

2. A Skilled Artisan Would Not Have Omitted 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 because it omits doxorubicin—it is limited to CVP.[11] McNeil does not teach that the anthracycline of CHOP should (or could) be omitted. In fact, it teaches the opposite.

Even were McNeil's teachings to have been considered in connection with LG-NHL instead of IG-NHL, Petitioner must live with the entirety of McNeil's teachings, not just the cherry-picked sentences. *See Panduit Corp. v. Dennison*

[11] CVP refers to cyclophosphamide (C), vincristine (V), and prednisone (P). Cyclophosphamide is an alkylating agent. Vincristine is a plant alkaloid. Prednisone is a steroid.

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"). And what McNeil teaches is the necessity of maintaining the anthracycline component of CHOP, *i.e.*, doxorubicin. In portions not cited by Petitioner'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, 004. 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.

In the prior IPR, the Board agreed with patent owner and rejected the petitioner's argument that "an ordinary artisan would have been prompted to modify McNeil's CHOP treatment to instead use the CVP treatment required by claim 1." Ex. 2001, 021. The Board also recognized the "suitability of CHOP for treating LG-NHL." *Id.*, 034.

As the Board explained, "given the prior art evidence of synergy between the doxorubicin component of CHOP and rituximab, viewed alongside McNeil's express teaching of reducing CHOP toxicity by performing mini-CHOP, Petitioner does not persuade us that an ordinary artisan would have omitted the doxorubicin

component of McNeil's CHOP, and instead used CVP therapy followed by rituximab as required by claim 1 of the '172 patent." Ex. 2001, 024; *id.*, 026 (same). The Board found this to be the case "even assuming that CVP therapy was known to be less toxic than CHOP." *Id.*, 019.

In spite of the Board's holdings, Petitioner repeats arguments made in the prior IPR and argues that skilled artisans reading McNeil would modify its CHOP regimen to change it to CVP because "a POSA concerned about doxorubicin's toxicity would have understood that CVP would be a better choice than CHOP for low-grade NHL." Pet. 55. Petitioner fails to cite any new evidence that should alter the Board's previous holding.

a. *CVP was not "both less toxic and equally effective as CHOP"*

First, Petitioner argues that "a POSA would have known that for low-grade NHL, CVP was both less toxic and equally effective as CHOP." Pet. 50; *see also id.*, 57. Petitioner relies on two references to make this argument, Bishop (Ex. 1006) and Dana (Ex. 1007).

Neither Bishop and Dana, however, supports Petitioner's argument. In particular, neither reference shows that CVP is less toxic than CHOP. In fact, Bishop reports that high-dose CAVP (a.k.a. CHOP) and CVP were found

"equitoxic," calling into question Petitioner's contention that CVP is less toxic than CHOP. Ex. 1006, 002. Dana also cannot support Petitioner's proposition because it does not even mention toxicity anywhere in the article. *See* Ex. 1007, 006 (discussing only overall survival data).

Petitioner's argument, that a POSA would know that CVP is better than CHOP for low-grade lymphoma as of the priority date, is belied by the fact that CHOP was still one of three "common…combination chemotherapies used to treat low-grade NHL," as acknowledged by Petitioner. Pet. 7-8. Indeed, a 1997 paper explained that "[t]he ***standard*** CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) was chosen for combination therapy with rituximab" in patients with LG-NHL. Ex. 2023, 001; Ex. 2024, 003 ("CHOP chemotherapy was chosen because this cytotoxic regimen is an effective first-line therapy for low-grade or follicular NHL.").

As of the priority date, the only published clinical results from using rituximab together with chemotherapy in lymphoma was rituximab in combination with CHOP. *See* Ex. 1020, 002. This study reported that the combination of rituximab and CHOP was highly effective in LG-NHL. Skilled artisans called the results "provocative" because it 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." Ex. 2021, 003. Therefore, the most relevant art strongly urged the use of CHOP with rituximab in low-grade lymphoma, further discouraging the skilled artisan from removing doxorubicin.

Importantly, the Board held in the previous IPR that "even assuming that CVP therapy was known to be less toxic than CHOP," Ex. 2001, 019, a skilled artisan would still not modify McNeil to omit doxorubicin because of "McNeil's express teaching that mini-CHOP can be used to reduce toxicity, alongside evidence in the art of synergy between rituximab and doxorubicin." Nothing Petitioner presents in this proceedings should disturb the Board's analysis and finding that doxorubicin would not be omitted from McNeil.

b. *Rituximab Was Known To Be Synergistic With Doxorubicin, Not The Components Of CVP*

Petitioner argues that skilled artisans would have thought that the known synergy between rituximab and doxorubicin would also be expected for rituximab and any other chemotherapy, including the individual components of CVP. Pet. 58. The record demonstrates otherwise.

Long before the August 11, 1999 priority date, it was known that one of "[t]he rationale[s] for combination of IDEC-C2B8 [rituximab] with CHOP" was "known synergy with doxorubicin." Ex. 2025, 002; *see also* Ex. 2023, 001 ("The standard CHOP regimen...was chosen for combination therapy with rituximab because...there is evidence of in vitro synergy between the antibody and doxorubicin.").

Petitioner points to 1995 and 1997 abstracts (Exhibits 1062 and 1063) by Dr. Myron Czuczman that refer to rituximab "synergy with chemotherapeutic agents," without identifying any chemotherapeutic agents in particular, as a reason why synergy would have been expected with any chemotherapy drug. Pet. 60. But by the priority date, this same author (Dr. Czuczman) had made clear in his full-length article that it was expected synergy between rituximab and doxorubicin that motivated the combination of rituximab and CHOP. Ex. 1020, 003 ("The rationale for the combination of Rituxan and CHOP includes … synergy with certain cytotoxic drugs, including doxorubicin."). If Dr. Czuczman thought rituximab would be synergistic with the non-doxorubicin components of CHOP, *i.e.*, CVP, he would have written so and not specifically identified doxorubicin as providing the synergy.

Petitioner asserts that uncited "publications discussing a possible synergy between doxorubicin and rituximab cite back to the Demidem study." Pet. 60. But the Demidem article does not teach that rituximab can be effective *in vitro* with ***all*** chemotherapeutic agents. Instead, the study showed that rituximab was able to sensitize a tumor cell line to two out of the three chemotherapeutic drugs tested (doxorubicin, cisplatin, and VP-16 [etoposide]). The other agents tested in Demidem were biologic cytotoxic agents, not chemotherapy (TNF-alpha, ricin, diphtheria toxin). The Demidem study did not test any of the components of CHOP other than doxorubicin.

The limited number of chemotherapy agents tested (three) in Demidem, together with the fact that not all of the chemotherapy agents tested showed synergy, *see* Ex. 1003, ¶63 (acknowledging there was no synergy with VP-16), would not indicate to a skilled artisan that rituximab could be synergistic with any chemotherapeutic agent, as Petitioner argues, or the never-before-tested drugs in a CVP regimen.

Importantly, nothing in the Demidem *in vitro* study changes the fact that skilled artisans understood that the provocative ***clinical*** results flowed, at least in part, from the synergy between rituximab and doxorubicin. Skilled artisans, who were clinicians, would have been guided by clinical results seen with doxorubicin,

and not omit doxorubicin based on an *in vitro* study that showed that rituximab might be synergistic with chemotherapy drugs other than doxorubicin.

Petitioner fails to cite any new evidence that should alter the Board's previous holding that skilled artisans would not modify the CHOP regimen taught by McNeil to omit doxorubicin, a drug known to be synergistic with rituximab.

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

Finally, 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, 003, but there is no disclosure that each dosing regimen given every 6 months should be four weekly doses of 375 mg/m^2.

Like its argument for Ground 3, Petitioner 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 Section VI.A.2, a skilled artisan would not have used the rituximab dosing regimen to treat relapsed disease as the dosing regimen for maintenance therapy.

As the Board held in the prior IPR, "relapsed patients…are beyond the scope of claim 1," Ex. 2001, 018, and the fact the weekly infusion amount for relapse disease is 375 mg/m^2 "does not demonstrate that a skilled artisan would have understood that those dosages were necessarily given" in a maintenance setting. *See id.*, 021 ("that the FDA-approved/recommended weekly rituximab dosage for relapsed or refractory LG-NHL might be the same as the dosage recited in claim 1 does not demonstrate that a skilled artisan would have understood that those dosages were necessarily given in [a clinical] study of intermediate grade NHL, a different patient population.").

Petitioner fails to cite any new evidence that should alter the Board's previous holding.

4. The Art Does Not Disclose Or Suggest The Specific Complete And Partial Responses Required By The Claim

As discussed in Section III.A, the Board construed Claim 1 as requiring a patient response prior to rituximab maintenance therapy according to "specific criteria for a complete response (CR) and a partial response (PR)." Ex. 2001, 006, citing Ex. 1001, 9:14-23 (describing specific clinical outcomes for CR and PR). Petitioner has failed to establish that the art disclosed or suggested this limitation.

VII. UNCONSTITUTIONALITY OF *INTER PARTES* REVIEW

In *Oil States Energy Services LLC v. Greene's Energy Group, LLC*, 639 F. App'x 639 (Fed. Cir. 2016), *cert. granted in part*, 2017 U.S. LEXIS 3727 (June 12, 2017), the Supreme Court will consider the constitutionality of *inter partes* review proceedings. Patent Owner preserves the position that this *inter partes* review proceeding and the challenge to Patent Owner's duly issued and existing '244 patent violates the Constitution by allowing for private property rights to be extinguished through an adversarial process in the Patent and Trademark Office, a non-Article III forum, without a jury. *See McCormick Harvesting Mach. Co. v. C. Aultman & Co.*, 169 U.S. 606, 609 (1898) (once a patent is granted, "[i]t has become the property of the patentee, and as such is entitled to the same legal protection as other property.").

VIII. CONCLUSION

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

Dated: July 10, 2017

Respectfully submitted,

/s/Michael Fleming

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, the undersigned certifies that on July 10, 2017, a copy of the foregoing document **BIOGEN, INC.'S PATENT OWNER PRELIMINARY RESPONSE** and **Exhibits 2001-29** have been served in its entirety via e-mail/FTP site, as agreed, on counsel of record for petitioners at the following address:

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

Pursuant to 37 C.F.R. § 42.24 (d), I certify that the present paper contains 13,972 words as counted by the word-processing program used to generate the brief. This total does not include the tables of contents and authorities, the caption page, certificate of service, or this certificate of word count.

Dated: July 10, 2017

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