UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.
Petitioner,

v.

BIOGEN, INC.
Patent Owner.

Case IPR2018-00285
U.S. Patent No. 8,329,172

PATENT OWNER RESPONSE

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I. INTRODUCTION

Low-grade non-Hodgkin's lymphoma (LG-NHL) is a cancer that grows more slowly than other lymphomas but is more deadly. It is incurable—even if patients suffering from LG-NHL respond to chemotherapy, they are plagued by repeated relapses and eventually die from the disease. Before the invention claimed in U.S. Patent No. 8,329,172 (the "'172 patent"), attempts to prevent such relapse with maintenance failed, and—in the words of Petitioner's expert—persons of ordinary skill had "abandoned" maintenance therapy.

The treatment regimen claimed in the '172 patent—CVP induction with rituximab maintenance given as four weekly doses of 375 mg/m^2 every six months for two years prolongs survival with minimal toxicity, and is now standard of care for LG-NHL patients.

This is the fourth *inter partes* review petition filed against the '172 patent. The Board denied institution on the first three petitions, but instituted this proceeding in a divided decision, noting "cogent arguments" in Patent Owner's Preliminary Response, but deciding to "evaluate both parties' arguments once the record is developed further during trial." *See* Paper 10 at 19.

Three of the four cited references in this IPR are identical to those from prior, denied petitions. In instituting this petition, however, the Board was unpersuaded that the non-identical reference, Hochster I (Ex. 1005), was cumulative of art it

previously rejected and declined to deny institution pursuant to Section 325(d). *See id.*, 022. There can now be no doubt that Hochster I is cumulative of the previously considered art and should likewise be rejected: Petitioner's expert conceded at deposition that the teaching of Hochster I is "the same" as Grossbard, a reference previously found to be unpersuasive by this panel in *Celltrion v. Biogen*, IPR2017-01093.

In any event, Petitioner's expert confirmed at deposition that "no prior art reference teaches" material limitations of the claim, including (i) "administering rituximab as four weekly doses of 375 milligrams per meter squared [mg/m^2] for maintenance therapy"; and (ii) "administration of rituximab every six months for two years for low-grade lymphoma." *See* Ex. 2051 (Dr. Robert Soiffer Depo. Tr.), 191:4-20. He also tacitly admitted that one of the references of the grounds, McNeil, suggests using only a single dose of rituximab, not four weekly doses, every six months for maintenance. He further did not disagree that even three years after the priority date, oncologists believed that further studies were needed to establish the treatment schedules for maintenance with rituximab. *See id.*, 183:13-23. And he admitted that "as of the priority date, it was not known what treatment schedule should be used for rituximab as maintenance therapy." *Id.*, 184:6-12.

Petitioner cobbles together disparate portions of different references for each claim element using impermissible hindsight, and fails to establish that a person

having ordinary skill in the art ("POSA") would have combined such references, or would have had a reasonable expectation of success in doing so.

Petitioner asserts, for example, that a POSA would have used four weekly rituximab infusions of 375 mg/m^2 as maintenance for chemotherapy responders with no relapsed disease because that was the only rituximab dosing that FDA had approved. But FDA approved that regimen only for ***induction*** therapy, which is different from maintenance, and only for ***relapsed-or-refractory*** patients. Recipients of rituximab treatment in the patent claim are neither relapsed nor refractory patients. They are partial or complete responders to prior chemotherapy who have not relapsed.

If a POSA would have tried using rituximab for maintenance in the claimed patient population, the POSA would have used a regimen less intensive (e.g., fewer infusions or less drug per infusion) than the regimen for induction. The FDA-approved dose was designed to induce responses in patients who have higher tumor burdens because they did not achieve partial or complete responses to prior therapy, or if they did, they subsequently relapsed.[1] The patients claimed in the '172 patent, by contrast, are chemotherapy responders who have lower tumor burdens because they have achieved such responses and have not relapsed. At deposition, Petitioner's

[1] Refractory patients are those who had been resistant to prior chemotherapy.

expert admitted this, Ex. 2051, 59:9-22, and he admitted that "therapies used as maintenance are usually ***less intensive*** than therapies used for induction." Ex. 2052 (Second Soiffer Depo. Tr.), 65:23-66:6.[2] .

Petitioner further argues that a POSA would have administered to the claimed patient population—people with LG-NHL—a maintenance dosing schedule (every six months for two years) being studied in a different patient population: elderly patients with ***intermediate-grade*** lymphoma (IG-NHL), as reported by McNeil. But that maintenance dosing schedule for IG-NHL had not even been reported to be successful. And even if it had been reported successful, disclosures related to IG-NHL do not apply to LG-NHL because, as Petitioner concedes, "the success or failure of a regimen in the context of intermediate-grade NHL ***says nothing*** about its success or failure in the context of LG-NHL, which is a different disease." Pet. 54. Petitioner's expert similarly admits that given "important differences [between IG-NHL and LG-NHL], treatments for different types of lymphomas were ***markedly different***." Ex. 1060 ¶35. The only plausible conclusion on this record is that a POSA would not look to McNeil's dosing schedule for IG-NHL patients when addressing the LG-NHL patients studied in Hochster I.

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[2] Emphasis is added to quotes unless otherwise noted.

Petitioner also fails to rebut evidence in the examination record of objective indicia of non-obviousness, including unexpected results. Petitioner's primary criticism of the evidence of unexpected results is that a clinical study reporting success with the claimed regimen, ECOG 1496, should not have used "observation," i.e., no maintenance therapy, as the control arm to compare with the rituximab-maintenance treatment arm. But Petitioner's own expert rejected this argument at deposition, testifying that the observation control arm was proper because "standard therapy at the time...would have been no maintenance" for "low-grade lymphoma." Ex. 2051, 104:17–105:4.

For these reasons, and further reasons articulated below, Petitioner's challenge fails and the Board should find that Petitioner failed to establish that Claim 1 is unpatentable.

II. BACKGROUND

A. Technical Overview

The sole patent claim is narrowly directed to treatment of LG-NHL with CVP to which the patient responds, followed by rituximab maintenance given as four weekly doses of 375 mg/m^2 every six months for two years. Ex. 1001, 22:56-64.

1. Non-Hodgkin's Lymphomas

Although sometimes referred to in singular form, NHL was known in 1999 as "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; Ex. 2054 (Declaration of

Dr. Leslie Oleksowicz in support of Patent Owner) ¶23. It was recognized that "[l]ow-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" characterized by rapidly-growing tumor cells. Ex. 1001, 4:49-52; Ex. 2054 ¶26. As Petitioner's expert acknowledges, "[g]iven these important differences, treatments for different types of lymphomas were markedly different." Ex. 1060 ¶35.

Moreover, successful use of a treatment for one type of lymphoma, such as IG-NHL, did not predict success for other types of lymphoma, like LG-NHL. Ex. 2054 ¶30. Indeed, Petitioner admits that "the success or failure of a regimen in the context of intermediate-grade NHL [IG-NHL] ***says nothing*** about its success or failure in the context of LG-NHL, which is a different disease." Pet. 54.

A successful treatment for NHL begins with "induction" therapy to induce a patient response. Ex. 2054 ¶27. Ideally, the patient will not subsequently relapse, but "LG-NHL is characterized by 'a pattern of continuing relapse with RFS [i.e., relapse-free survival] of only 2 to 3 years' following chemotherapy" induction. Ex. 1060, ¶40, citing Ex. 1010, 007. In contrast, IG-NHL was frequently cured by first-line therapy (eliminating the possibility of any relapse). Ex. 2054 ¶27.

2. Maintenance For LG-NHL

Therapies designed to prevent relapse in patients who respond to induction are called "maintenance" therapies. Ex. 2054 ¶31. At the time of the invention, there was a significant unmet medical need for effective maintenance to maintain remission of LG-NHL. *Id.* ¶32. Chemotherapies that were successful as induction therapies were not successful as maintenance therapies. *Id*. Similarly, biologic drugs, such as interferon, had been tried as maintenance but were unsuccessful. *Id.* As Petitioner's expert conceded, chemotherapy and interferon maintenance for LG-NHL had been "abandoned" by practitioners because of intolerable toxicity and insufficient evidence of any benefit. Ex. 2051, 110:13–111:2.

Given the absence of any successful maintenance therapy before the priority date, the standard of care for responders to induction therapy was, as conceded by Petitioner's expert, no further treatment before relapse. Ex. 2051, 104:17–105:4; Ex. 2054 ¶32.

3. Rituximab

Rituximab is a monoclonal antibody that binds to the CD20 antigen on normal and cancerous B-cells, facilitating their destruction. Ex. 2054 ¶33. Approximately two years before the priority date, the FDA approved rituximab as monotherapy to re-induce responses in relapsed-or-refractory low-grade lymphoma patients.

Ex. 1001, 1:47-50. Rituximab was not approved as maintenance, nor was there any information on its effectiveness in a non-induction setting. Ex. 2054 ¶34.

B. Earlier IPR Petitions

Over the past several years, the Board has denied institution of three IPRs against the '172 patent, including one filed by Petitioner, IPR2017-01166, and two filed by other parties: IPR2015-00418 and IPR2017-01093. The art and arguments in this current proceeding are substantially the same as those rejected previously. The Ground references McNeil, Maloney, and alleged "Rituxan Labels" were all cited in prior IPR proceedings filed by other petitioners. *See* Paper 10 at 21.

The petitioner in IPR2017-01093 relied on Grossbard (Ex. 2039) instead of Hochster I (Ex. 1005), but the latter is cumulative. The Board was not persuaded at the institution stage, Paper 10 at 22, but at deposition, Petitioner's expert expressly conceded that the teaching of Hochster I is "the same" as Grossbard. *See* Ex. 2051, 181:4-23 (agreeing that the "Grossbard commentary" has "the same disclosure [he] relied on from the Hochster [I] abstract reference" and that he does "not rely on any disclosure from the Hochster [I] reference…that is not contained in this Grossbard commentary article"). In view of this, the Board should reach the same substantive conclusions as in IPR2017-01093 based on Grossbard.

In IPR2017-01093, the Board found that no reference "disclose[d] or suggest[ed] the rituximab maintenance therapy dosing regimen required by claim 1

of the '172 patent." Ex. 2042, 020. The Board further found that there was insufficient evidence that a POSA "would have sought to treat LG-NHL patients with the same rituximab dosing regimen employed in a study of a wholly different patient population—namely, elderly patients having aggressive non-Hodgkin's lymphoma that is responsive to CHOP chemotherapy." *Id.*, 020-21. The Board also found insufficient evidence that a POSA would have "used, or had a reasonable expectation of success in using, a rituximab dose of 375 mg/m^2" weekly for four doses following CVP induction in LG-NHL because "the best dose and schedule of rituximab remain to be established." *Id.*, 021. The Board should reach similar conclusions here, especially in view of the admissions by Petitioner and its expert.

III. PETITIONER FAILED TO ESTABLISH THAT HOCHSTER I, MALONEY, MCNEIL, AND OTHER KEY REFERENCES QUALIFY AS PRINTED PUBLICATIONS.

Petitioner has failed to carry its burden to establish that Hochster I, Maloney, McNeil, and other key references on which it relies were publicly accessible before the priority date. The status of an exhibit as a printed publication cannot be assumed. As Judge Harlow has explained, "[w]hether a reference qualifies as a printed publication is a statutory requirement that goes to the heart of our patentability analysis." Paper 10, Dissent at 2, 4 (emphasizing "the centrality of the printed publication analysis to the ultimate success of [] patentability challenges").

Petitioner made no attempt to show actual dissemination of these references. Rather, Petitioner argued that they were publicly accessible based on cataloguing and indexing. Petitioner's showing is inadequate for at least the following reasons:

First, Petitioner did not even contend—let alone submit any evidence—that the journal *articles* it relies upon were catalogued and indexed as of the priority date. Instead, Petitioner argued—but failed to show—that journal *issues* containing those articles, among others, were cataloged and indexed. Pet. 30-31, 37. Petitioner relied solely on MARC records as purported evidence of such cataloging and indexing. *Id.* As Petitioner's declarant Dr. Hall-Ellis testified, however, a MARC record simply catalogs a serial title. *See* Ex. 2053, 110:5-8. "[I]t is not the purpose of the MARC record to indicate anything about a specific journal issue" and "[i]t does not do so." *Id.*, 73:2-4.

Second, Petitioner failed to establish that any of the libraries from which it allegedly obtained Hochster I, Maloney, McNeil, or the PDR made such materials available to the public before the priority date. Even if it had presented evidence that the materials were cataloged and indexed by the libraries, Petitioner still would have needed to show "technical accessibility"—e.g., that the materials had been shelved for access by patrons. *Acceleration Bay v. Activision Blizzard*, 2017-2084, slip op. at 12 (Fed. Cir. Nov. 6, 2018); *In re Bayer*, 568 F.2d 1357, 1359-62 (CCPA 1978) (focusing not only on cataloging, but also shelving). Instead of attempting to do so,

both Petitioner and Hall-Ellis erroneously took the position that cataloging and indexing alone would be sufficient, if proven. *See* Pet. 29; Ex. 1016 ¶13 ("I understand that cataloging and indexing by a library is sufficient[.]"). Petitioner contended that "[a] MARC record…indicates that" each reference was "publicly accessible in at least one library by" a particular date. Pet. 30-31, 37. But as noted above, a MARC record does not "indicate anything about a specific journal issue," including when it was shelved. Ex. 2053 at 73:2-4. Nor does it report when a text like the PDR was shelved. *Id.*, 116:24–117:3.

The petition makes no mention of any date stamps on Hochster I, Maloney, McNeil, or the PDR, but even assuming that each reference was date stamped by a library on the day that it was received, Petitioner would still bear the burden of establishing that each reference was then shelved, or otherwise made available for inspection, at that particular library before the priority date to show technical accessibility. As Hall-Ellis confirmed at deposition, libraries "do not follow identical shelving practices." *Id.*, 64:5-7.

Accordingly, Petitioner fails to meet its burden of establishing that Exs. 1003, 1005, 1008, and 1039 constitute prior art printed publications.

In denying Petitioner's prior petition, the Board held that the evidence was insufficient to establish that Exhibit 1004 is a printed publication because "the record [was] devoid of evidence concerning the availability of the Rituxan Label from the

FDA website (or elsewhere) prior to the critical date." Ex. 2044, 011-13. The present petition is "substantially the same" as the prior petition, Pet. 12, and the record here is similarly devoid of such evidence. *See* Pet. 33.

In denying Petitioner's prior petition, the Board likewise held that Petitioner did "not present evidence sufficient to show...that the Rituxan Webpage [here, Ex. 1041] was in fact publicly accessible." Ex. 2044, 014-15. Here, Petitioner tries to rely on the Hall-Ellis declaration to establish that the Rituxan Webpage was available on Genentech's website per the Internet Archive, but Hall-Ellis is not competent to testify regarding the Internet Archive. Ex. 2053, 128:21–133:5; 135:22-25; *cf. IBM v. Intellectual Ventures II*, No. IPR2015-00089, Paper No. 44, 53-54 (PTAB Apr. 25, 2016) (relying on a "Butler Affidavit" from "the Office Manager of the Internet Archive, which includes the Wayback Machine service").

IV. PERSON OF ORDINARY SKILL

As of the August 11, 1999 priority date, a POSA would have been a practicing oncologist or hematologist with at least an M.D. degree and 1-3 years of experience treating NHL patients. *See* Ex. 2054 ¶¶15-21.

V. PETITIONER FAILS TO ESTABLISH THAT THE CLAIM IS 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, 1069 (Fed. Cir. 2012). Here, the subject matter is medicinal treatment, which is an unpredictable art. *In re Efthymiopoulos*, 839 F.3d 1375, 1380 (Fed. Cir. 2016).

The combination of Hochster I, McNeil, and Maloney or alleged "Rituxan Label" references does not render obvious Claim 1.[3]

A. The Cited References Do Not Disclose Or Suggest The Responses Required By The Claim

Petitioner's obviousness argument fails at the outset because none of the cited art discloses the limitation "CVP therapy to which the patient responds" as construed by the Board.[4]

The Board construed the phrase "CVP therapy to which the patient responds" as requiring that the patient "responds according to the criteria set forth in the '172 patent." Paper 10 at 7 (citing Ex. 1001 at 9:14–23, which provides specific criteria for a complete response and partial response, and distinguishes patients with such

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[3] Petitioner describes alleged "Rituxan label" references—Ex. 1004, Ex. 1039, and Ex. 1041—as "substantively identical," Pet. 2, and claims that Maloney (Ex. 1008) "contains the same relevant information as the Rituxan™ label." Pet. 1. This section, therefore, addresses these references together.

[4] "Both parties agree with this construction." Paper 10 at 7.

responses from "non-responders"). Those criteria define the clinical requirements for complete and partial responses as follows (Ex. 1001, 9:14-23):

> ***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.

None of the alleged prior art discloses such clinical requirements for responses, let alone teaches administering maintenance to a patient who so responds to CVP. Ex. 2054 ¶¶72-78. Accordingly, Petitioner has failed to demonstrate that the claim element "CVP therapy to which the patient responds" is found anywhere in the cited art such that the claim is obvious. *See Medtronic v. Barry*, 891 F.3d 1368, 1377 (Fed. Cir. 2018) (upholding PTAB's non-obviousness finding because petitioner "failed to cite to any particular passage or figures from [an alleged prior art reference] that 'explicitly disclosed'" the claim limitation); *Elbit Systems of*

America v. Thales Visionix, 881 F.3d 1354, 1357 (Fed. Cir. 2018) (finding that "[s]ubstantial evidence support[ed] the PTAB's conclusion of nonobviousness" in part because the claim limitation was not "explicitly disclosed" in the art).

Petitioner argues that the "CVP to which a patient responds" limitation is inherent in Hochster I because, "by definition," maintenance "necessarily requires" that patients responded to CVP induction. *See* Pet. 40. But as Petitioner's expert conceded, as of the priority date, maintenance was not given only to responders. Rather, it was also given to certain non-responders (e.g., patients with stable disease), who are indisputably outside the claim scope. Ex. 2051, 176:12-16 (agreeing that in "prior art publications, maintenance therapy could be given to patients with stable disease after induction therapy"); Ex. 2054 ¶¶76-78.

In any event, Claim 1 does not merely require that the patient responds; rather, it requires that the patient "respond according to the criteria set forth in the '172 patent." Paper 10 at 7. Hochster I does not disclose any such criteria or any such response. Ex. 2054 ¶¶72-78. The Board should therefore reject Petitioner's argument.

B. Petitioner Fails To Establish A Reason Or Motivation To Modify Or Combine The Cited References To Practice The Invention

Petitioner fails to establish that a POSA would have combined (1) McNeil's "every 6 months for 2 years" dosing schedule for elderly **IG-NHL** patients following

CHOP chemotherapy, with (2) Hochster's distinct patient population of patients with **LG-NHL** following CVP chemotherapy, using (3) Maloney's or alleged "Rituxan Label" references' *induction* dosing regimen of four weekly of 375 mg/m^2 for relapsed-or-refractory disease as the regimen for *maintenance* therapy in the claimed patient population of partial or complete responders "according to the criteria set forth in the '172 patent."

1. Petitioner Fails To Establish That A POSA Would Have Used Four Weekly Doses Of 375 mg/m^2 As Maintenance

a. The Alleged Prior Art Does Not Specify Any Amount Of Rituximab For Maintenance

None of the cited art specifies any amount of rituximab, let alone four weekly doses of 375 mg/m^2, to be given every 6 months for maintenance therapy, as claimed. Ex. 2054 ¶¶83-88. Petitioner's expert conceded this at deposition. Ex. 2051, 191:4-15.

Only Hochster I and McNeil contain any reference to maintenance. Ex. 2054 ¶84. Hochster I simply mentions "anti-CD20 maintenance," without identifying any anti-CD20 antibody in particular, much less a dosage or schedule. *Id.* McNeil reports the launch of a study that included a rituximab maintenance regimen designed for elderly IG-NHL patients in which rituximab would be given "every 6 months for 2 years," but fails to disclose a rituximab dosage amount. Ex. 1003, 005.

b. McNeil Suggests Using Only A Single Dose Of Rituximab, Not Four Weekly Doses, Every 6 Months For Maintenance

McNeil not only fails to disclose using four weekly doses of 375 mg/m^2 for maintenance, it suggests ***different*** maintenance dosing. Ex. 2054 ¶¶85-88. A POSA would have understood McNeil's reference to "Rituxan every 6 months for 2 years" to refer to a ***single*** dose of rituximab, not four weekly doses, given every 6 months. *Id.* Petitioner's expert conceded as much when posed with an analogous hypothetical during deposition:

> Q. If a dose of Agent X is given weekly for eight doses for induction and there is the disclosure of administering Agent X every six months thereafter, would a POSA understand that a dose of X is given every six months after the last induction dose and then another dose is given 12 months after the last induction dose and so forth?
>
> A.·…I think, the answer to that is, yes….

Ex. 2051, 31:20-32:8 (objections omitted). Here, although rituximab induction therapy was given weekly for four doses in the art, a POSA would have understood McNeil's disclosure of administering rituximab every 6 months for 2 years to mean that a single dose of rituximab is given at each six-month interval. Ex. 2054 ¶86.

c. Rituximab Dosing Was A "stumbling block," And "it was not known what treatment schedule should be used for rituximab as maintenance therapy"

At the time of the invention, dosing rituximab was, according to the literature, a "stumbling block[]" for skilled artisans, and "the best dose and schedule of rituximab remain[ed] to be established," even for existing uses (much less untried uses such as maintenance). Ex. 2039, 010; Ex. 2054 ¶89. Petitioner's expert testified that he did not disagree with this literature. Ex. 2051, 178:13-18. Petitioner's expert also acknowledged that even three years ***after*** the priority date, skilled artisans were still emphasizing that "[f]urther study is needed to establish treatment schedules [for rituximab], such as maintenance therapy after remission induction." Ex. 2026, 005; Ex. 2051, 183:13-23 (testifying that he had no reason to disagree with this statement). Petitioner's expert conceded that "as of the priority date, it was not known what treatment schedule should be used for rituximab as maintenance therapy." Ex. 2051, 184:6-12. This evidence belies Petitioner's assertion that a POSA would have considered four weekly doses of 375 mg/m^2 for maintenance obvious. Ex. 2054 ¶¶89-90.

d. A POSA Would Not Have Used An Amount Of Rituximab Approved For Induction Of Relapsed-Or-Refractory Patients As Maintenance For Patients Who Responded And Had Not Relapsed.

Petitioner argues that a POSA would have used four weekly doses of 375 mg/m^2 for maintenance because that rituximab amount is disclosed in

Maloney and alleged "Rituxan Label" references. *See* Pet. 26. As acknowledged by Petitioner's expert, however, these references recommended four weekly doses of 375 mg/m^2 only for ***induction*** therapy in relapsed and refractory patients, not as ***maintenance*** therapy. *See* Ex. 2051, 191:4-15 (acknowledging that no prior art reference taught administering four weekly doses of 375 mg/m^2 for maintenance); Ex. 2054 ¶91-93. Indeed, the word "maintenance" appears nowhere in Maloney or alleged "Rituxan label" references. *See id*.

Moreover, the claimed patient population is ***neither relapsed nor refractory***. Rather, as the Board previously found, members are complete or partial responders to prior therapy (meaning they were not refractory to such therapy) with no intervening relapse. *See* Ex. 2001, 018 (holding that "relapsed patients…are beyond the scope of claim 1").[5]

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[5] In prior IPR proceedings, the Board denied institution due to insufficient evidence that a POSA supposedly would have been encouraged to use the 4 x 375 mg/m^2 dosing in a patient population distinct from that described in the FDA-approved indication. *See* Ex. 2042, 021 (holding that there is insufficient evidence "why an ordinarily skilled artisan would have used, or had a reasonable expectation of success in using, a rituximab dose of 375 mg/m^2" in the claimed regimen); Ex. 2001, 024 (same).

Petitioner fails to establish that a POSA would have believed the amount of rituximab used for inducing a response in relapsed and refractory patients was appropriate for ***maintenance*** every six months in patients who responded to induction therapy and had not relapsed. If anything, the evidence shows a POSA would have used a "less intensive" dosing regimen for maintenance.

Petitioner's reliance on *Pfizer v. Apotex* to argue that a dosing regimen "approved by the FDA" is obvious is misplaced. In *Pfizer*, the issue before the court was whether a "chemist at the time would simply make known pharmaceutically-acceptable salts of whatever active ingredient with which he or she was working at the time." *Pfizer v. Apotex*, 480 F.3d 1348, 1362 (Fed. Cir. 2007). Based on the facts before it, the court found a POSA would use known salts to create new chemical compounds. The decision does not suggest it would be obvious in the context of a method-of-treatment patent to use a known dosing regimen from a different disease context. Indeed, the Federal Circuit has held the exact opposite. *See Eli Lilly v. Teva Pharms.*, 619 F.3d 1329, 1338 (Fed. Cir. 2010) (holding that it was not obvious to use a drug for one patient population in another population because the infringer "was not able to show a credible connection between the" two different treatment settings); *Am. Hospital Supply v. Travenol Labs.*, 745 F.2d 1, 7 (Fed. Cir. 1984) (holding it was not obvious to use a therapy for "a different class of users with specific unique nutritional problems.").

(1) Petitioner's Expert Admitted That Maintenance Regimens Are Usually "less intensive" Than Induction Regimens

If anything, a POSA would have been motivated to treat the claimed patients with a ***less intensive*** rituximab regimen than the four weekly 375 mg/m^2 regimen for inducing a response in relapsed-or-refractory patients. Ex. 2054 ¶¶94-95. Petitioner's expert testified that, as of the priority date, "therapies used as maintenance are usually less intensive than therapies used for induction." Ex. 2052, 65:23–66:6.[6] This remains true today. As Cancer.net, the website created by the American Society of Clinical Oncology (ASCO),[7] explains: "Maintenance therapy often uses traditional chemotherapy drugs[,] [b]ut doctors give ***lower doses*** than when you first have treatment." Ex. 2038, 001.

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[6] This testimony from Petitioner's expert, Dr. Soiffer, was made in another IPR proceeding between the Parties involving rituximab. The priority date of the patent at issue in that IPR proceeding is the same as the '172 patent: August 11, 1999.

[7] ASCO is one of the largest and most well-known organizations of oncologists in the United States. Ex. 2051, 83:11-25.

(2) *Maintenance Regimens Are Less Intensive Than Induction Regimens Because The Tumor Burdens Of Maintenance Patients Are Lower.*

One reason maintenance regimens are less intensive, i.e., lower doses or fewer infusions, is because the tumor burden is significantly lower in the maintenance setting, or even nonexistent in the case of a complete response. Ex. 2054 ¶96.

Maloney and the alleged "Rituxan Label" references disclose use of four weekly doses of 375 mg/m^2 to induce a response in relapsed-or-refractory patients, i.e., as induction therapy.[8] Ex. 2054 ¶97. Patients in need of induction generally have higher tumor burdens because they are treatment naïve, failed to achieve responses to prior therapies, or responded and have relapsed. *Id.* The patients claimed in the '172 patent, by contrast, have lower tumor burdens because they have achieved complete or partial responses and have not relapsed. *Id.*

At deposition, Petitioner's expert agreed that "responders have lower tumor burdens because they have achieved complete or partial responses and have not relapsed." Ex. 2051, 52:22–53:6; *id.,* 59:9-22 (agreeing that "patients who are

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[8] Induction therapy is treatment given to induce a clinical response. Ex. 2054 ¶ 27. Ex. 2051, 29:21-23. This would include the FDA-approved dosing regimen of four weekly doses of 375 mg/m^2 to induce a response in patients with relapsed-or-refractory disease.

relapsed-or-refractory" are "nonresponders" and "have higher tumor burdens than responders"); *id*., 44:8-10, 56:18-24 (accord).

A POSA would have understood that patients with lower tumor burdens would naturally require less rituximab to attack their fewer tumors—particularly given that rituximab kills tumor cells by binding to them directly. Pet. 4 ("'IDEC-C2B8 (Rituximab)'…'binds [to] the CD20 antigen with high affinity' and 'efficiently kills CD20+ cells.'"); Ex. 2054 ¶98. In other words, a POSA would have appreciated that the total amount of rituximab needed to bind to tumors is proportional to the total number of tumors that need to be destroyed.[9] Ex. 2054 ¶98.

This proportionality is reflected by pharmacokinetic data in Petitioner's cited reference, which shows that rituximab serum levels in LG-NHL patients after a dose are inversely proportional to their tumor burdens.[10] *Id.* ¶¶99-100. The higher the tumor burden, the more rituximab drops out of circulation by binding to and

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[9] A rituximab antibody cannot bind more than two anti-CD20 antigens (because each antibody has two binding arms). Ex. 2054 ¶98. After binding, the rituximab antibody is not recycled back into circulation following cell lysis. *See id*.; Ex. 2051, 47:9-13.

[10] Serum levels are the amount of unbound rituximab in blood circulation. Ex. 2051, 36:14-17.

destroying those tumor cells—i.e., the tumors act as "sinks," sequestering rituximab from the blood and reducing its serum concentration. *Id.*; 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."). At deposition, Petitioner's expert agreed that more tumor cells will require more rituximab antibody for binding, and conversely, "with less tumor burden, there will be more rituximab in the serum" that is unbound. *See* Ex. 2051, 38:7-17; *id.*, 37:14-21 (explaining a POSA would presume that "more tumor cells equals more antibodies bound and less free antibody in the serum"). Petitioner's expert also conceded that rituximab's pharmacokinetic information "might suggest that" "lower tumor burden requires less rituximab to be effective." *Id.*, 50:7-20.

(3) *Relapsed-And-Refractory Patients Are "more resistant to therapy"*

Furthermore, a POSA would have used a less intensive regimen of rituximab as maintenance therapy because, as acknowledged by Petitioner's expert at deposition, the four weekly doses of 375 mg/m^2 were designed for relapsed-or-refractory patients, who were known to be "more resistant to therapy." *See* Ex. 2051, 57:2-4. For maintenance treatment of the claimed responders, who have less resistant (if any) disease, a POSA would have used a less intensive dosing regimen. Ex. 2054 ¶¶101-02.

A POSA would therefore have believed that if rituximab was used as maintenance for responders with no disease relapse, then a rituximab regimen less intensive than the four weekly 375 mg/m^2 regimen for relapsed-or-refractory patients should be used. *See id.* As Petitioner's expert acknowledged, regimens less intensive than four weekly doses of 375 mg/m^2 had been successfully used for low-grade lymphoma. Single infusions of 10, 50, 100, and 250 mg/m^2; and four weekly doses of 100 and 250 mg/m^2 had been successfully used for low-grade lymphoma. Ex. 2051, 154:1–155:8, 156:22– 157:15 (conceding that in a prior-art clinical trial for rituximab, "[t]here were no differences in efficacy for doses of 125, 250 and 375 milligrams per meter squared" in terms of response rates).

(4) ***Petitioner's Reliance On Safety Data From Studies In Relapsed-Or-Refractory Patients Is Misplaced.***

Petitioner does not dispute that to the extent a POSA would have been inclined to use rituximab for maintenance, the pharmacokinetic data disclosed in the alleged "Rituxan label" references would suggest using a ***lower*** rituximab amount than that used for relapsed-or-refractory disease. Instead, Petitioner asserts that such data "does not amount to teaching away" because it supposedly points to such lower dosing only as an "alternative" to the dose for relapsed-or-refractory patients. Pet. 48. Petitioner tries to justify that assertion by arguing that the alleged "Rituxan

label" references teach that "'[t]here has been no experience with overdosage in human clinical trials,' even at a higher '500 mg/m^2' dose." *Id*., 26, 48.

But all of the human clinical trials discussed in the alleged "Rituxan label" references were trials in relapsed-or-refractory patients. Ex. 1004, 001 ("Clinical Studies"); Ex. 2054 ¶¶103-105. This is not informative of the safety impact of administering four weekly 375 mg/m^2 repeatedly for two years as maintenance therapy in responding patients with lower tumor burdens. *Id.* Moreover, the "500 mg/m^2" dose Petitioner relies on was in "single doses," not four weekly doses, in patients with relapsed-or-refractory disease. Ex. 1004, 001; Ex. 2054 ¶¶103-05. The alleged "Rituxan label" references do not report any study evaluating the safety of doses greater than four weekly doses of 375 mg/m^2 even for patients with relapsed-or-refractory disease. *See id.*

As discussed above, patients who experienced complete or partial responses with no disease relapse, as claimed, have lower tumor burdens than relapsed-or-refractory patients. And lower tumor burdens result in higher serum rituximab levels, as discussed above. Petitioner fails even to assert, let alone cite evidence, that a POSA would have believed administering four weekly doses of 375 mg/m^2 to patients with low tumor burdens would produce serum rituximab levels that are just as safe as the levels observed with the same dose in relapsed-or-refractory patients with higher tumor burdens. Ex. 2054 ¶104; Ex. 2051, 47:24–48:11 (agreeing that it

was observed in the prior art that "higher rituximab serum level [equates to] more drug activity"). Accordingly, the Board should reject Petitioner's argument that the Maloney and alleged "Rituxan label" references taught that administering four weekly doses of 375 mg/m^2 every six months as maintenance would be a safe option.

Petitioner's assertion that it would have been obvious to administer repeatedly the relapsed-or-refractory rituximab regimen for maintenance therapy, without any analysis or discussion of differences between treatment of relapsed-or-refractory patients and the responders claimed in the '172 patent, exposes Petitioner's impermissible hindsight-driven approach to obviousness. Ex. 2054 ¶¶103-05. 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. v. Tetra Pak Cheese & Powder Sys.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013).

(5) *Petitioner Fails To Identify A Single Example Of An Induction Regimen Used As Maintenance.*

Petitioner also argues that the rituximab induction regimen for relapsed-or-refractory patients would have been used as a repeating maintenance regimen because "prior maintenance therapies (e.g., CVP) had likewise been given 'at the same drug dosages' that were used for first-line induction therapy." Pet. 48. As alleged support, Petitioner cites only a single reference: Portlock (Ex. 1025). *See* Pet.

48. But Portlock did not use its first-line induction regimen as maintenance therapy. Ex. 2054 ¶¶106-10.

In Portlock, the first-line induction regimen comprised administering "6-17 cycles" of CVP "every 21-28 days" followed by "four consolidation cycles…at 21-28 day intervals," for a total of about 10 to 21 cycles (over 7 to 20 months) of CVP. Ex. 1025, 002. The "maintenance CVP" regimen,[11] by contrast, involved only a ***single*** cycle of CVP "repeated every 3 months." *See id.* Thus, Portlock administered ***less*** CVP to patients as recurring maintenance therapy (1 cycle) than it did as first-line induction therapy (10 to 21 cycles), a less intensive regimen. Ex. 2054 ¶¶106-10. The reference in Portlock to "maintenance CVP (at the same drug dosages)" simply indicates that each cycle of CVP during maintenance was the same dosage amount as each cycle during induction. *See* Ex. 2051, 64:7-18 (testifying that "[t]he maintenance regimen was a single cycle of CVP repeated every three months"). But the number of cycles differed dramatically. Portlock did not repeatedly administer 10 to 21 cycles of CVP as maintenance. Ex. 2054 ¶107.

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[11] In this study, only "complete responders" received "maintenance CVP" while partial responders continued on non-maintenance CVP "until tumor progression occurred or until psychosocial factors intervened." *Id.*; Ex. 2054 ¶108.

Citing Maloney and the alleged "Rituxan Label" references, Petitioner is arguing the ***entire*** induction regimen in those studies—four weekly doses of 375 mg/m^2—would be repeatedly given as maintenance therapy. Portlock does not support this argument. *Id.* ¶¶ 106-10.

At deposition, Petitioner's expert conceded that in Portlock, "[l]ess CVP was given to patients as recurring maintenance therapy than was used as first line induction therapy." Ex. 2051, 64:7-18. Other references likewise disclosed maintenance therapies that used ***less*** of an agent than was used for induction. *See e.g.,* Ex. 2018, 002, Fig. 1 (studying interferon dose of 5 MU/m^2 as first-line induction, and a dose of 2 MU/m^2 as maintenance); Ex. 2054 ¶109. Petitioner's expert also testified at deposition that lower doses of interferon were used as maintenance compared to induction doses. *See* Ex. 2051, 62:2-5 (agreeing that "[l]ower doses of interferon were given for maintenance therapy compared to doses given for induction").

Thus, using an induction dosing regimen as the recurring maintenance regimen, as claimed in the '172 patent, was not obvious. If anything, a POSA would have used, in the words of Petitioner's own expert, a "less intensive" dosing regimen for maintenance.

e. Petitioner's Obvious-To-Try Argument Fails.

Petitioner argues that the "four weekly doses of 375 mg/m^2" limitation "would have been at least obvious to try." Pet. 45. But the obvious-to-try doctrine does not apply to individual claim limitations; it applies to claimed inventions as a whole. *KSR Int'l v. Teleflex*, 550 U.S. 398, 419, 421 (2007) (finding that "a patent claim" can be proved obvious "by showing that the combination of elements was '[o]bvious to try'"); *Kahn v. Gen. Motors*, 135 F.3d 1472, 1480 (Fed. Cir. 1998) (explaining that the obviousness analysis must be done for the "invention…as a whole and the claims must be considered in their entirety."). Even Petitioner's own obvious-to-try case makes this clear. *See Bayer Schering Pharma AG v. Barr Labs*, 575 F.3d 1341, 1347 (Fed. Cir. 2009) (addressing criteria for evaluating when only "an invention" would or would not have been obvious to try).

Even if the obvious-to-try doctrine were applicable to an individual limitation, Petitioner fails to establish that the elements of the doctrine—as articulated by Petitioner itself—would be satisfied here. For example, Petitioner fails to establish that "the prior art provides direction about 'which parameters were critical'" in developing a ***maintenance*** for LG-NHL using rituximab, or "'which of many possible choices is likely to be successful'" such that it could be said that the prior art "reduces the options to a set that is 'small [and] easily traversed.'" Pet. 45-46 (quoting *Bayer*, 575 F.3d at 1347); Ex. 2054 ¶82.

Petitioner also argues that the "four weekly doses of 375 mg/m^2" limitation "would have been at least obvious to try" because "Patent Owner acknowledged that the prior art 'showed that the dosing [of rituximab] had been optimized as 4 doses.' Ex. 1022, 016." Pet. 45-46. But that "acknowledgement" was made with respect to induction, not maintenance. Indeed, the pending claim at issue, claim 49, was "[a] method of treating low grade or follicular non-Hodgkin's lymphoma," not maintenance of complete or partial responders with no disease relapse. Ex. 1022, 015 (citing a study by Grillo-Lopez, Ex. 2029, in which 4 doses "were found to be effective" in ***relapsed*** patients); Ex. 1022, 010 ("Grillo-Lopez et al. refer to treatment of relapsed NHL in patients…."); Ex. 2054 ¶93.

f. Petitioner's Argument That "The Claimed Dose Falls Within A Range Disclosed In the Prior Art, And Is Thus Obvious" Fails.

Petitioner argues that Maloney "disclosed that rituximab had been tested in at least doses of 100, 125, 250, and 500 mg/m^2," which was a disclosure of "a range that includes the claimed dose." Pet. 47. But Maloney discloses only "single doses up to 500 mg/m^2," not "four weekly doses," as claimed in the '172 patent. Ex. 1008, 001; Ex. 2054 ¶111. Thus, the Maloney and alleged "Rituxan label" references do not disclose a range encompassing the claim limitation of ***four weekly doses*** of 375 mg/m^2. *Id.*

Moreover, Petitioner is again improperly arguing that a claim ***element***, *i.e.*, "the claimed dose," can be rendered *prima facie* obvious. But the obviousness analysis must be conducted for the "invention…as a whole and the claims must be considered in their entirety." *Kahn*, 135 F.3d at 1480. Petitioner does not—and could not—contend that Maloney or alleged "Rituxan label" references disclose a range of maintenance therapies for LG-NHL patients who had complete or partial responses to CVP without relapse, let alone that the claimed dosing regimen of four weekly doses of 375 mg/m^2 every 6 months for two years falls within that range.

2. Petitioner Fails To Establish That A POSA Would Have Given Rituximab Every Six Months For Two Years For LG-NHL Patients

None of the art cited by Petitioner teaches administering rituximab every six months for two years as a maintenance schedule for LG-NHL, as claimed. Ex. 2054 ¶¶112-15. Petitioner's expert conceded this at deposition. *See* Ex. 2051, 191:16-20.

Only one reference cited by Petitioner allegedly even mentions the use of anti-CD20 maintenance in LG-NHL—Hochster I (Ex. 1005)—and that reference

does not contain any disclosure of what anti-CD20 agent to use,[12] let alone any dosing regimen. Ex. 2054 ¶113.

Petitioner argues that the claim limitation requiring administration of rituximab maintenance to LG-NHL patients "every 6 months, [] wherein the maintenance therapy is provided for 2 years" is satisfied by combining Hochster I with the teachings of McNeil, a news article reporting the start of a clinical trial in elderly patients with IG-NHL. *See* Pet. 49-52. In the alternative, Petitioner argues that even if a POSA would not have combined McNeil with Hochster I, it was obvious to give rituximab maintenance using a schedule of every six months for two years. *See* Pet. 50. Neither argument has merit.

a. Petitioner Fails To Show That A POSA Would Have Used McNeil's Rituximab Dosing Schedule In The Patient Population Of Hochster I

Neither Petitioner nor its expert establish any scientific or clinical rationale why a POSA allegedly would have used the rituximab dosing schedule from McNeil, which treated elderly patients with IG-NHL following CHOP induction chemotherapy, in the Phase III study proposed by Hochster I, which involved a

[12] Exhibit 1005, in fact, discloses another anti-CD20 antibody successfully used in a clinical study, not rituximab. Ex. 1005, 007 (describing a successful study with "I-131-labeled anti-CD20 antibody").

different patient population (patients with LG-NHL and an unknown age range) following a different induction chemotherapy (i.e., CF or CVP). Pet. 39.

(1) *McNeil's IG-NHL Dosing Regimen "says nothing" About An Appropriate Dosing Regimen For LG-NHL Patients*

Petitioner's argument that a POSA would have applied McNeil's dosing schedule to the patient population of Hochster I ignores the fact that a POSA would have understood IG-NHL and LG-NHL as different diseases that should be treated differently. Ex. 2054 ¶¶116-26.

Hochster I proposes treating patients with LG-NHL, a type of lymphoma that is incurable and characterized by constant relapse. *Id.* McNeil discloses a rituximab dosing schedule for a different set of patients, patients with IG-NHL (a curable disease). *Id.* These references address different diseases in different patient populations understood to require different treatments. *Id.*

In prior IPR proceedings, this Board twice rejected petitioner arguments that "an ordinary artisan would have been prompted to modify McNeil's treatment of patients with IG-NHL to instead treat the LG-NHL required by claim 1 of the '172 patent." Ex. 2001, 021; Ex. 2042, 020-021 (same). The Board recognized—and the record showed there, as here—that IG-NHL and LG-NHL were known to be materially different in disease tumor growth, relapse rate, remission, prognosis, and therapies. *Id.*

Petitioner's expert acknowledges that "[o]ne of the central determining factors for a patient's prognosis as of August 1999 was the patient's 'grade' of lymphoma: low, intermediate, or high." Ex. 1060 ¶35; Ex. 2054 ¶¶120-21. LG-NHL tumors "grow more slowly" than IG-NHL and HG-NHL tumors. *Id.* But IG-NHL patients, unlike LG-NHL patients, were "frequently curable." *Id.* Petitioner's expert concedes that "[g]iven these important differences [between IG-NHL and LG-NHL], treatments for different types of lymphomas were ***markedly different***." *Id.*

Moreover, relevant art at the time showed that POSAs knew IG-NHL and LG-NHL patients responded differently to drug treatment. *See, e.g.*, Ex. 2009, 001 ("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."); Ex. 2054¶123.

Most patients with IG-NHL were cured with chemotherapy and therefore did not relapse. *See, e.g.,* Ex. 1013, 010 ("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%"); Ex. 2054 ¶125. In contrast, almost all patients with LG-NHL continuously relapsed until succumbing to the disease. *See, e.g.*, Ex. 2003, 002

("[F]inal disease eradication cannot be achieved in low-grade lymphomas…."); Ex. 2027, 002 ("Relapse [] is the rule."); Ex. 2002, 004 (same); Ex. 2054 ¶125.

A POSA also would have known that even with an initial response to chemotherapy, relapses occurred faster with IG-NHL than with LG-NHL. Ex. 2054 ¶124; *compare* Ex. 2051, 213:9-21 (testifying that "average time to relapse is probably 6 to 12 months" for IG-NHL patients) *with* Ex. 1060 ¶40 (averring that LG-NHL patients relapse "'2 to 3 years' following chemotherapy").

Nowhere does Petitioner establish that a POSA would have looked to McNeil for a dosing schedule to treat LG-NHL patients. To the contrary, Petitioner admits that a POSA would not have found McNeil's dosing regimen informative for LG-NHL—even if the regimen had been successful in IG-NHL. Petitioner concedes that "the success or failure of a regimen in the context of intermediate-grade NHL ***says nothing*** about its success or failure in the context of LG-NHL, which is a different disease." Pet. 42 (citing and endorsing the Board's prior decision articulating the same). Petitioner's expert similarly states that "the success or failure of a particular regimen in the context of treating intermediate-grade NHL ***does not imply that the same result will occur*** in treating LG-NHL, which is a different disease." Ex. 1060 ¶113. Because the success or failure of a regimen in IG-NHL does not inform whether the same regimen would be successful or harmful in LG-NHL, McNeil does

not provide any motivation or reason for a POSA to use an every-six-months-for-two-years schedule in the Hochster LG-NHL patient population. Ex. 2054 ¶114.

Federal Circuit precedent makes clear that absent a sufficient connection between disparate patient populations, prior art disclosing a drug regimen in one patient population does not render obvious a patent claiming the same regimen in a different patient population. *See, e.g.*, *Eli Lilly*, 619 F.3d at 1338; *Am. Hospital Supply*, 745 F.2d at 7.

(2) *McNeil's Rituximab Dosing Schedule Was Used After CHOP Induction, Not After CVP or FC Induction, As Used In Hochster I*

Not only do Hochster I and McNeil address different grades of NHL, they are directed to different induction chemotherapies. CHOP was used as induction in McNeil, while FC or CVP was used in Hochster I. *See* Ex. 1003, 005; Ex. 1005, 009; Ex. 2054 ¶¶127-28. At deposition, Petitioner's expert questioned the effectiveness of rituximab maintenance following rituximab-based induction, characterizing his own testimony as implying that "differences in induction therapy can impact whether Rituximab maintenance therapy will be effective." Ex. 2051, 109:4-8.[13]

[13] Petitioner's expert did not deny that this was also known as of the priority date. *See* Ex. 2051, 109:9-16.

Petitioner offers no explanation why a POSA supposedly would have used a maintenance regimen designed to follow CHOP induction to treat patients who received CVP induction instead. Ex. 2054 ¶¶127-32. This is especially troublesome considering rituximab was "known [to have] synergy with doxorubicin," which is a component of CHOP but not of FC or CVP. *Id.*; Ex. 2025, 002; Ex. 2023, 001; Ex. 2051, 111:3–112:19 (agreeing there was data "which suggested that there was synergy between doxorubicin [in CHOP] and Rituximab," but not for components of CVP or FC).

A POSA would have known that in the context of chemotherapy combinations, "synergistic combination[s] [between agents]…could result in reduced drug doses." Ex. 2040, 002; *see* Ex. 2036, 001 (explaining that because "[s]orafenib and metformin synergistically decreased the proliferation of [thyroid cancer] cell lines… [a] combined treatment enabled a significant dose reduction of sorafenib"); Ex. 2037, 001 (explaining that "[t]riptolide prodrug synergizes with reduced dose standard of care (gemcitabine and nab-paclitaxel) and helps in reducing the doses of these [standard of care] toxic drugs"); Ex. 2054 ¶131. Petitioner's expert agreed that, as of the priority date, it was "known that some synergistic combination could result in a reduced dose of one drug compared to the dose for that drug when used alone" when tested in vitro, i.e., in "cell line" experiments. Ex. 2051, 115:8-13. Moreover, a POSA would have known that such

a reduced dose could take the form of fewer or less frequent administrations. Ex. 2054 ¶¶131-32. Yet Petitioner contends, without analyzing the issue, that a POSA would have used the same number of maintenance doses of rituximab, with the same frequency, after both CHOP induction with the synergistic doxorubicin component, and CF/CVP induction without it.

Neither Petitioner nor its expert provides any underlying scientific or clinical rationale why a POSA would have used McNeil's rituximab dosing regimen for the Hochster I study despite differences in lymphoma type and induction therapy. Petitioner's ground for challenge therefore fails.

b. It Was Not Obvious To Give Rituximab Every Six Months As Maintenance To LG-NHL Patients

Petitioner argues that even without McNeil, POSAs would have known that rituximab maintenance should be given every six months for two years, as required by the '172 patent claim. But Petitioner and its expert reach this conclusion through hindsight and by inappropriately relying on the ECOG 1496 protocol, which is not part of the record in this case and which petitioners have repeatedly failed to establish as a printed publication.

At deposition, Petitioner's expert indicated that he, "[i]n an indirect way," relied on his personal knowledge of "the E1496 protocol" in concluding that the Hochster I abstract would have taught a POSA the rituximab maintenance dosing regimen. *See* Ex. 2051, 98:3-13; 182:1-25 (testifying he "assumed that the ECOG

1496 protocol" would have been publicly accessible, and that he "relied on that assumption" for his opinions). This is improper because (1) the ECOG 1496 protocol is not part of the record in this case and was not cited by Petitioner or its expert, and (2) the Board has twice rejected attempts by petitioners to establish any ECOG 1496 protocol as a printed publication because there is insufficient evidence of public accessibility. *See* Ex. 2001, 008; Ex. 2042, 012, 016. Here, Petitioner did not even attempt to establish any ECOG 1496 protocol as a printed publication. This Board should reject Petitioner's challenge because it is not based only on "prior art consisting of patents or printed publications," as required by statute. *See* 35 U.S.C. § 311(b).

Petitioner argues that POSAs would have administered rituximab maintenance every six months because one study reported that "'B-cell recovery began at approximately six months following completion of treatment.'" Pet. 26 (citing Ex. 1006, McLaughlin). Notably, this Board rejected this very same argument in a prior IPR brought by a different petitioner, holding that the "B-cell depletion observed" argument raised by petitioner "appears to be based on improper hindsight." Ex. 2001, 031-32. Petitioner implicitly concedes in a footnote that its argument is based on a publication from 2009 explaining why "Patent Owner selected a six-month frequency of rituximab maintenance." Pet. 50, n.7, citing Ex. 1029, 006 (a 2009 publication). This Board rejected such hindsight, pointing out that

"§ 103(a) expressly states that '[p]atentability shall not be negatived by the manner in which the invention was made.'" Ex. 2001, 031.

Absent reliance on post-priority-date statements in hindsight, Petitioner's argument does not withstand scrutiny for several reasons. First, the study on which Petitioner relies for "B-cell recovery" data reports B-cell levels after the use of rituximab as induction for relapsed-or-refractory patients, not administration of rituximab as maintenance after a patient responds. Ex. 2054 ¶¶133-34. Petitioner fails to establish that a POSA would have believed that B-cell recovery time in patients receiving rituximab for maintenance would be the same as recovery time for patients who received rituximab for relapsed-or-refractory disease. *Id.*; Ex. 2051, 207:11-18 (testifying that patients with non-relapsed disease have a "first response [that] is generally more durable" compared to relapsed patients).

Second, Petitioner's argument relies on the B-cell recovery data for ***normal*** B-cells, not cancerous ones. Ex. 2054 ¶135; Ex. 1004, 001. In the study that produced this data, cancerous B-cells did not repopulate in the relapsed and refractory patients until ***13 months*** after treatment with rituximab. Ex. 2054 ¶135; Ex. 1006, 005 ("[T]he projected median time to progression for responders is 13.0 months."); Ex. 2051, 31:14-18 (agreeing that "progression…is the emergence of new tumor cells"). Petitioner fails to explain why POSAs supposedly would have

designed a schedule for maintenance dosing based on the time it allegedly takes for normal B-cells, as opposed to cancerous B-cells, to recover.

Petitioner also argues POSAs would have given rituximab maintenance every six months because it had been reported that "'[r]ituximab was detectable in the serum of [LG-NHL] patients three to six months after completion of treatment.'" Pet. 26 (citing Ex. 1004, 001). But this argument also lacks merit for several reasons. First, as a threshold matter, Petitioner fails to establish that a POSA would have designed a maintenance schedule for LG-NHL based on drug detectability in the serum. Ex. 2054 ¶¶136-39. Moreover, the evidence indicates that a POSA would not have designed such a maintenance schedule that way. *Id.* Petitioner's expert conceded at deposition that he was not "aware of any drug in the prior art that was tested for maintenance therapy in low grade lymphoma and dosed based on drug detectability levels." Ex. 2051, 146:17-21. It simply was not done. Ex. 2054 ¶¶136-39. Second, even assuming that a POSA would have used drug detectability to design a maintenance schedule for LG-NHL, if the range of detectability is "three to six months," then a POSA would have chosen to administer rituximab every ***three*** months, not every ***six*** months, so that the maintenance dosing regimen could benefit everyone, including patients whose rituximab blood levels drop more quickly. Ex. 2054 ¶136. At deposition, Petitioner's expert agreed that administering

rituximab every six months would result in patients with no measurable rituximab before each dosing interval. *See* Ex. 2051, 119:13-24; Ex. 2054 ¶136.

Confronted with questions challenging his reliance on the recovery of normal B-cells and on drug detectability levels as the bases for his opinion that a POSA would have been motivated to use rituximab every six months for maintenance of LG-NHL patients, Petitioner's expert tried to cobble together an entirely new theory during deposition. In particular, he stated for the first time that "the predominant reason to treat at six months is a clinical reason to prevent 90 percent of patients from recurring," based on data from the McLaughlin clinical trial that he says shows 10% of patients relapsing at 6 months (Exhibit 1006). *See* Ex. 2051, 133:19-21; 142:10-13 (same).[14] But this, too, is based on hindsight. As an initial matter, it is not clear, when viewing Figure 1 of the McLaughlin paper, whether relapse was prevented in 80% or 90% of patients at six months. Ex. 2054 ¶¶140-43. But even assuming that the number is 90%, there is no evidence that anyone in the art had ever designed a maintenance dosing schedule so that 10% of patients would relapse. *Id.* Petitioner's expert conveniently relies on 90% as the target in this proceeding

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[14] Designing a treatment interval that provides a dose when 90% of patients have not progressed means that 10% of patients would have relapsed before the next maintenance dose. *See* Ex. 2051, 129:5-18.

because the claim requires dosing every 6 months and he reads the data in McLaughlin as showing that relapse was prevented in 90% of patients at 6 months. *Id.* He is working backward from the claim, not forward from the state of the art at the time.[15] Again, this theory is nowhere to be found in either the Petition or Petitioner's expert declaration.

Moreover, the expert's new theory does not make any logical sense. If a POSA would have used time to progression in the McLaughlin clinical study (Figure 1 of Exhibit 1006) to design a maintenance dosing regimen, then the POSA would have picked an every-three-months maintenance schedule (or more frequently) because 0% of patients progressed in the McLaughlin clinical study at 3 months. Ex. 2054 ¶142; Ex. 2051, 146:25–147:3 (agreeing that "Figure 1 shows that no patients relapsed at three months"); *id.,* 148:21–149:4 (agreeing that according to the McLaughlin data, "if a POSA wanted to try to treat every patient before relapse, you would pick three months"). All other things being equal, it is illogical to assume that a POSA would have chosen a dosing schedule that would result in ***more*** relapses. Ex. 2054 ¶¶ 140-43.

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[15] Indeed, the ***cited*** reference in Petitioner's Ground, Maloney (Ex. 1008), shows that relapse was prevented in 90% of patients at 4 months, not 6 months. *Id.*, 010.

The Board should reject Petitioner's shifting narrative on why a dosing schedule of every six months for low-grade lymphoma was obvious.

c. It Was Not Obvious To Give Rituximab For Two Years As Maintenance

Petitioner further argues that "it would have been obvious to administer rituximab maintenance therapy as long as possible to maintain remission, including for at least two years." Pet. 5. But this conclusory argument fails to account for what a POSA would have understood to be significant safety risks associated with such prolonged B-cell depletion. Ex. 2054 ¶144.

Petitioner's expert acknowledges that B-cells are a critical and necessary component of our immune systems. *See* Ex. 2051, 28:3–29:20 (agreeing that B-cells and the antibodies they produce are each "critical components of a person's immune system"); Ex. 2033, 004; Ex. 2054 ¶145.

As discussed in Section V.B.2.b above, Petitioner alleges that POSAs would have believed that administering rituximab every six months would prevent any normal "B-cell recovery." Pet. 50; *see also* Ex. 2051, 138:24–139:4 (agreeing that a POSA would have "assum[ed]" that "if a regimen were designed to give Rituximab every six months, B-cell levels would be zero for at least 50 percent of patients"); *id.,* 131:4-24 (testifying that "average" and "median [B-cell] count was zero at six months" in the McLaughlin clinical study).

A POSA would have known that prolonged B-cell depletion carries with it a risk of fatal infections. Ex. 2054 ¶¶146-51. Petitioner fails to explain why a person of ordinary skill would nonetheless have been motivated to design a rituximab maintenance dosing regimen to keep B-cell levels at zero for at least two years. *Id.* The risk of infection would have been especially concerning in the context of chemotherapy induction followed by maintenance, as most chemotherapy regimens, including FC and CVP, have their own risk of fatal infections. *Id.*; Ex. 2051, 91:24–92:1 (agreeing that "FC and CVP have risk of fatal infections"). Hochster I, for example, reported that half of the first eight patients treated in its phase I/II study developed infections. Ex. 1005, 009.

Petitioner never even addresses this issue, much less offers an explanation why, prior to the invention, a POSA would have believed it safe or advisable to deplete a patient's B-cells for more than two years. Instead, Petitioner argues that rituximab maintenance for ***two years*** would have no safety issues because ***single*** courses of rituximab (e.g., four weekly doses) had been shown to be safe. *See* Pet. 26. But administering repeated courses of rituximab as maintenance for two years presents fundamentally different safety concerns. Ex. 2054 ¶148. At deposition, Petitioner's expert conceded that long-term B-cell suppression meant that "patients would not recover their B-cells," and therefore "might be subjected to lower,

certainly, lower immunoglobulin levels and they might have a higher incidence of infection long-term." Ex. 2051, 135:17–136:2.

Indeed, a POSA would have understood that the difference between short-term versus long-term, continuous suppression of normal B-cell levels is stark. Ex. 2054 ¶149. There was evidence that relatively short-term suppression of B-cells with rituximab was tolerable because antibody levels would not be greatly reduced with a single course of rituximab in the induction setting. *Id.* But there was concern that if normal B-cell levels were never allowed to recover, then antibody levels would fall to dangerous levels, thereby immunocompromising the patient. *Id.*

There was simply no safety data at the time of the invention about possible toxicities and unintended effects, such as infections, with complete B-cell depletion for two years using any therapy, let alone rituximab. Ex. 2054 ¶150; Ex. 2051, 136:20–137:8 (testifying that he did not know of any "publically available data before the priority date concerning prolonged B-cell suppression for two years or more"). Indeed, Petitioner's expert acknowledged that the closest analogy was in "patients with inherited B-cell deficiencies," and those patients' "severe B-cell toxicity [was] associated with infection." Ex. 2051, 125:5-11. Petitioner fails to explain why a POSA would be motivated to give rituximab every six months for two years given the safety risks involved. Ex. 2054 ¶150.

In addition to ignoring the tremendous safety risk of long-term, continuous B-cell suppression, Petitioner also fails to explain why a POSA supposedly would have thought that giving rituximab maintenance for two years or longer would have been more beneficial than a shorter duration of maintenance. Ex. 2054 ¶151. At deposition, Petitioner's expert testified that the issue of "whether or not maintenance therapy is given indefinitely or for a period of time" "would depend to a great extent on either data that comes from either a randomized trial or data that comes from a single arm Phase II trial or perhaps expert opinion in terms of trials that may be ongoing." Ex. 2051, 32:9-24. Petitioner failed to address any of these variables, instead opting for the extraordinary conclusion that a POSA would simply have closed his or her eyes and given maintenance indefinitely. Ex. 2054 ¶¶144-51.

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

In its institution decision, the Board relied on the opinions of Petitioner's expert that there would have been a reasonable expectation of success. But at deposition, Petitioner's expert testified that he applied a legally incorrect standard for reasonable expectation of success. He presumed that there is a reasonable expectation of success even when there is "not a likelihood[,] necessary, but a ***possibility*** that maintenance Rituxan would provide a better outcome than observations and that it would be safe." Ex. 2051, 246:23–247:6. Controlling case law makes clear that reasonable expectation of success requires more than just a

"possibility." *Medichem v. Rolabo*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) ("[T]o have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one ***possibly*** arrived at a successful result"); *Eli Lilly*, 619 F.3d at 1338 (explaining that a prior art reference disclosing a "bare proposal to use" a drug is insufficient).

None of the art cited by Petitioner provides a reasonable expectation of success for rituximab maintenance as claimed by the '172 patent. Ex. 2054 ¶¶152-55. Indeed, only two references in Petitioner's Grounds, Hochster I and McNeil, even mention the use of an anti-CD20 antibody as maintenance. *Id.*

Hochster I fails to provide any support for Petitioner's assertion that there was a reasonable expectation of success for using rituximab as maintenance for LG-NHL. *Id.* Hochster I reports only that the authors proposed "conducting phase III study of CF vs. CVP ± anti-CD20 maintenance"; it provides no results or data of any kind. *Id.*; Ex. 1005, 009. This mere suggestion to study rituximab maintenance in LG-NHL cannot provide a reasonable expectation of success.[16]

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[16] Petitioner argues that the patent specification "'adds nothing beyond the teachings of' Hochster I." Pet. 44. But this relies on Petitioner's mischaracterization that the "Hochster I's disclosure 'is identical to the ['172] patent itself.'" *Id.*, 43. This is

Given the unpredictability in the field and the fact that Hochster I fails to specify any rituximab maintenance regimen, much less disclose any results, these references cannot establish a reasonable expectation of success. Ex. 2054 ¶152-55. The prior art teaches merely to pursue a "general approach that seemed to be a promising field of experimentation" or "gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988); *Medichem*, 437 F.3d at 1167.

Petitioner's conclusory argument that there would have been a reasonable expectation of success also fails to address (1) the fact that no successful maintenance had been established for LG-NHL; (2) the disclosure of using an every-six-months-for-two-years schedule for IG-NHL "says nothing about its success or failure in the context of LG-NHL"; (3) safety concerns with using a dosing regimen alleged to continuously suppress normal B-cell levels; and (4) antigen-escape concerns with recurrent rituximab administrations. *Id.*

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demonstrably false. The specification discloses the rituximab maintenance regimen claimed, "Rituximab maintenance therapy (375 mg/m^2 weekly times 4 every 6 months for 2 years," Ex. 1001, 13:14–16, whereas Hochster I does not disclose ***any*** dosing regimen.

1. No Successful Maintenance Had Been Established For LG-NHL In The Prior Art

As of the priority date, the field was replete with maintenance-therapy failures, rebutting Petitioner's contention that a POSA would have had a reasonable expectation of success in developing an efficacious maintenance treatment.

Despite the efforts of many, no maintenance had been shown to effectively maintain remission and prevent relapse of LG-NHL. Ex. 2054 ¶¶156-60. 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. As admitted by Petitioner's expert, "standard therapy" as of the priority date did not include maintenance. *See* Ex. 2051, 104:17–105:4; *see also id.*, 70:20–71:1 (accord). Indeed, Petitioner's expert testified that the practice of maintenance for low-grade lymphoma had been "abandoned" by the priority date. *See* Ex. 2051, 110:13–111:2 (testifying that "CVP, continued CVP and Interferon…were not considered, particularly successful. So they were abandoned.").

Both chemotherapy and interferon were abandoned by the priority date because there was no real evidence of any benefit and both were associated with intolerable toxicities. Ex. 2054 ¶¶158-71. Petitioner's expert testified that maintenance with chemotherapy "by the mid '80s, wasn't being done at all" because of "an essential belief that this regimen did not prevent people from relapsing." Ex. 2051, 69:1-11; Ex. 1060 ¶40 (testifying that attempts at chemotherapy maintenance

also "often ha[d] resulted in more toxicity"). Petitioner's expert also testified that, as of the priority date, "there was no convincing evidence that Interferon was beneficial," Ex. 2051, 104:17–105:4, and it had "considerable toxicity." *Id.*, 74:4-11.

The many failures with attempted maintenance in LG-NHL 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."). After so many failures, the mere announcement of a new maintenance study without any results, as in Hochster I and McNeil, simply cannot support a reasonable expectation of success. Ex. 2054 ¶159-60.

Contrary to Petitioner's claims, the description in Hochster I of a proposed "Phase III" clinical study does not provide a reasonable expectation of success. Ex. 2054 ¶¶159-63. As Petitioner's expert conceded at deposition, "many Phase III studies fail," Ex. 2051, 81:13-15, and there was no prior clinical experience "using rituximab or any other anti-CD20 drug as maintenance therapy before the priority date." *Id.,* 99:2-8.

2. No Reasonable Expectation Of Success For Administering Rituximab Every Six Months

Petitioner relies solely on the disclosure of McNeil to argue that there would have been a reasonable expectation of success using "a six-month frequency and two-year duration" of rituximab maintenance in low-grade lymphoma patients. *See* Pet. 49. Not so.

McNeil reported only the commencement of a study; it provided no results or data of any kind. Ex. 2054 ¶¶172-74. As Petitioner's expert agreed at deposition, McNeil provided only "speculat[ion]" 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."[17] Ex. 2051, 106:19–107:2; Ex. 1003, 001. As the Board held in connection with a previous IPR petition, the fact that prior art "suggest[s] 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 id.*, 026-27 (same).

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[17] The clinical study referenced by McNeil would ultimately show that the proposed rituximab maintenance schedule was not effective after R-CHOP induction therapy in IG-NHL. Ex. 2058, 001 ("After R-CHOP, no benefit was provided by MR [rituximab maintenance].").

Petitioner never explains why, much less offers evidence that, a POSA reviewing McNeil would have had any reasonable basis to believe that the every-six-months-for-two-years rituximab maintenance in IG-NHL patients who received CHOP induction would actually work. Ex. 2054 ¶¶172-74. And even if it did, Petitioner admits that "the success or failure of a regimen in the context of IG-NHL ***says nothing*** about its success or failure in the context of LG-NHL, which is a different disease." Pet. 54. Accordingly, McNeil does not support Petitioner's reasonable-expectation-of-success arguments.

3. No Reasonable Expectation Of Tolerable Toxicity For Keeping B-Cell Levels At Zero For Two Years

As discussed in Section V.B.2.b above, Petitioner alleges that skilled artisans would have believed that giving rituximab every six months would prevent any normal "B-cell recovery." Pet. 50; *see* Ex. 2051, 138:24–139:4. But Petitioner fails to establish that skilled artisans would have believed that B-cell levels of zero for two years or more would have involved tolerable toxicity. Ex. 2054 ¶¶175-79. To the contrary, there would have been serious concerns about the risk of fatal infections. *Id.*

As discussed in Section V.B.2.c, there was no experience with using therapy to continuously suppress B-cell levels for two years or more with any drug, let alone rituximab. Ex. 2054 ¶176. Because B-cells are critical components of a patient's immune system, skilled artisans would not have expected that keeping B-cell levels

at zero long-term would have been safe. *Id*. As discussed in Section V.B.2.b, Petitioner's conclusory argument that safety data with a single course of rituximab would provide a reasonable expectation of success with long-term B-cell suppression should be rejected.

Indeed, Petitioner's expert conceded that skilled artisans would "probably" be concerned about greater infections with "long-term B-cell suppression." Ex. 2051, 136:15-19. And Petitioner's expert acknowledged that the closest analogy was in "patients with inherited B-cell deficiencies," and those patients' "severe B-cell toxicity [was] associated with infection." *Id.,* 125:5-11. Petitioner fails to explain why a POSA would have a reasonable expectation of success administering a rituximab dosing regimen that allegedly keeps B-cell levels at zero for two years or more. Ex. 2054 ¶__.

4. Petitioner Fails To Address Antigen Escape

Petitioner fails to address another reason why a POSA would have been skeptical about successfully using rituximab as maintenance in LG-NHL: reported antigen escape with repeated rituximab treatments in LG-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. Ex. 2054 ¶¶175-79. It was first observed before the priority date that the "potential for tumor transformation with loss of CD20 expression may prevent recurrent

treatment." Ex. 2020, 002. Others similarly published their doubts that rituximab could be successfully used as maintenance because of the antigen escape problem: "Maintenance therapy [with rituximab] is also being explored, ***although antigen escape may limit its use***." Ex. 2021, 006. Petitioner's expert acknowledged that "antigen escape was a known issue" that would have had "the potential to limit the effectiveness" of rituximab maintenance. Ex. 2051, 79:9-25. Petitioner fails to address the issue of antigen escape and its impact on prospects of success of rituximab as maintenance. Ex. 2054 ¶¶180-82.

VI. OBJECTIVE INDICIA

A. Satisfaction of Long-Felt Need

As of the priority date, there was a long-felt need in the field to prolong progression-free and overall survival of low-grade patients with maintenance that was effective and had tolerable toxicity. Ex. 2054 ¶¶184-87. At the time, "no single chemotherapy regimen ha[d] been considered to provide a definitive progression-free survival (PFS) or overall survival (OS) advantage" for LG-NHL in the prior decades. Ex. 1029, 001. As discussed in Section V.C.1, attempts at developing maintenance with chemotherapy and interferon were unsuccessful due to lack of efficacy and intolerable toxicity and, in the words of Petitioner's expert, were "abandoned" by the priority date.

The long-felt need for maintenance that could provide an improvement in survival with minimal toxicity in LG-NHL was satisfied by the claimed invention, which became the "new standard" for patients with low-grade lymphoma, as discussed further below. Ex. 1029, 007; Ex. 2054 ¶¶185-87; Ex. 2051, 174:11–175:13 (agreeing that "rituximab maintenance is a…standard for patients with low grade lymphoma").

Petitioner does not dispute that a need existed for effective maintenance, but instead argues that this need was "long-felt" because Rituxan was FDA approved a year and nine months before the priority date. *See* Pet. 62-63. The Board should reject Petitioner's argument for several reasons.

First, Petitioner's contention that long-felt need should be calculated from Rituxan's availability date relies on a misinterpretation of *Newell v. Kenney Mfg.*, 864 F.2d 757, 768 (Fed. Cir. 1988). In *Newell*, the court found that prior-art rendered obvious claims to a do-it-yourself adjustable window shade that did not require tools, *id.* at 766, and that there was no long-felt need after a prior artist invented a tearable material that solved "the problem of having to cut the [shade]." *Id.*, 768 (explaining that "once another supplied the key element, there was no long-felt need or, indeed, a problem to be solved by [the inventor]."). The *Newell* decision does ***not*** stand for the proposition that long-felt need is calculated from the date that an element of the invention becomes available.

To the contrary, case law is clear that "long-felt need is analyzed as of the date of an articulated problem and evidence of efforts to solve that problem." *Texas Instruments v. U.S. ITC*, 988 F.2d 1165, 1178 (Fed. Cir. 1993). Here, the lymphoma literature states that no therapy in the prior ***decades*** before the priority date had provided "a definitive progression-free (PFS) or overall survival (OS) advantage" for LG-NHL. Ex. 1029, 001; Ex. 2057, 002 ("The major controversy is whether any treatment can induce long-term disease-free survival and alter the natural course of the disease."); Ex. 2054 ¶184.

Second, Petitioner's argument that a nearly two-year period of need is not "long-felt" is legally incorrect.[18] "[T]he law imposes no per se floor on the length of time needed to establish a long-felt need in the art." *Securitypoint Holdings v. United States*, 129 Fed. Cl. 25, 45 (2016). Rather, "[t]he circumstances of each individual obviousness determination are unique and are to be viewed as such by the finder of fact." *Id*. Here, there was an urgent need for therapy that could improve patient survival. Ex. 2054 ¶¶184-87. Given the urgency and importance of the need, even

[18] Petitioner is also incorrect that rituximab was available only as of November 1997. Petitioner's expert conceded at deposition that "Rituximab was available for clinical study before it was FDA approved." Ex. 2051, 164:16-18.

the two-year period between FDA approval of Rituxan and the priority date should be considered long-felt. *Id.*

B. Unexpected Results

As the Patent Office found during prosecution, the claimed invention of the '172 patent demonstrated unexpected results. *See* Ex. 1024, 008. Since the priority date, published data in the literature shows that the claimed method of using rituximab maintenance prolongs overall survival and progression-free survival "to a far greater extent than achieved by any prior strategy and with minimal toxicity." Ex. 2054 ¶¶188-94.

These results were unexpected because, as discussed in the previous Section, no treatment in the prior decades had shown definitive survival improvement for LG-NHL. *See id.*; Ex. 1029, 001; Ex. 2057, 002. The claimed invention changed this paradigm by showing that maintenance with rituximab can increase survival with minimal toxicity in low-grade lymphoma patients, and has since become the new standard of care. Ex. 2054 ¶¶188-94.

The benefits of the claimed invention were first reported in a Journal of Clinical Oncology (JCO) article submitted as Exhibit 1029 ("Hochster II"), which reported results from the ECOG 1496 clinical trial. *See* Ex. 2051, 102:2-6 (agreeing "that the effectiveness of the claimed method was studied in the ECOG 1496 clinical trial."); Ex. 2054 ¶190. The ECOG 1496 study was part of a collaboration "with

IDEC Pharmaceuticals Corporation [predecessor of the patent owner] to explore Rituximab treatment in other indications." Ex. 2059, 009-10.

Petitioner's expert agreed that JCO is a prestigious, peer-reviewed clinical journal that publishes articles with "conclusions [] supported by the data." Ex. 2051, 144:11-14. And that in general, "JCO only publishes studies the reviewers think advance the state of knowledge." *Id.*, 144:15-20.

As reported in Hochster II, the claimed invention "demonstrated prolongation of PFS [progression-free survival] for MR [Rituximab maintenance] treated patients with median of more than three times longer and a 60 percent reduction in progression risk." Ex. 2054 ¶192 (quoting Ex. 1029, 005). This survival improvement was to "a far greater extent than achieved by any prior strategy and with minimal toxicity." *Id*. (quoting Ex. 1029, 007). This study showed benefit in progression-free survival in "all patient subsets receiving MR [maintenance rituximab]." *Id.* (quoting Ex. 1029, 005). Petitioner's expert agrees that these conclusions are supported by the data. *See* Ex. 2051, 169:1–171:13.

While not sufficiently powered to show statistical significance of overall survival, the ECOG 1496 results "show[ed] a positive trend" in overall survival for patients receiving the claimed treatment. Ex. 2054 ¶193 (quoting Ex. 1029, 005). This trend was especially convincing in the subset of "patients with high tumor burden." *Id.* The reason for the lack of statistical significance in overall survival was

due to "immaturity of the data with a small number of events, inclusion of patients with low tumor burden, sample size, mix indolent histologies and the efficacy of secondary treatment with Rituximab in the OBS [observation] arm." *Id.* Again, Petitioner's expert does not dispute these conclusions. *See* Ex. 2051, 171:14–173:9.

To address the underpowered trend showing an improvement in overall survival, others have since conducted additional studies to determine whether rituximab maintenance actually improves overall survival in patients with LG-NHL. Ex. 2054 ¶194. As Petitioner's expert agreed, the literature shows that the claimed rituximab maintenance regimen does improve overall survival. Specifically, a meta-analysis[19] published in 2017 titled "Rituximab maintenance improves overall survival of patients with follicular lymphoma—Individual patient data meta-analysis," combined the results from multiple randomized clinical trials, including ECOG 1496, to determine if rituximab maintenance improved overall survival. Ex. 2050, 001-02; Ex. 2054 ¶194. The article concluded that "maintenance Rituximab improves overall survival consistently in all patients regardless of patient and disease characteristics compared with observation." Ex. 2050, 002. Petitioner's

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[19] A meta-analysis combines data from multiple studies in an effort to increase power to determine whether trends in individual studies are statistically significant. Ex. 2051, 158:4-159:24.

expert agreed with this conclusion, Ex. 2051, 222:10-16, and agreed that this conclusion was applicable for the ECOG 1496 regimen claimed by the '172 patent. *Id.*, 229:8-17. This evidence of improvement in overall survival further shows why rituximab maintenance for low-grade lymphoma is standard of care today. Ex. 2054 ¶194.

1. The ECOG 1496 Study Appropriately Used Observation As The Comparison Arm

Petitioner argues that the Patent Office was incorrect to conclude there were unexpected results because the ECOG 1496 study used observation, instead of a different maintenance regimen, as the control arm. *See* Pet. 59-60. But Petitioner's own expert rejected this argument at deposition. He testified that an observation control arm was "reasonable" because "maintenance therapy with chemotherapy and Interferon was not used in practice." Ex. 2051, 230:23–231:6. Petitioner's expert acknowledged that "standard therapy at the time...would have been no maintenance" for "low-grade lymphoma." *Id.*, 104:17–105:4; *see also id.*, 110:13–111:2 (testifying that attempts at maintenance with chemotherapy and interferon "were abandoned."); Ex. 2054 ¶¶195-97.

2. Confirming The Authors' Hypothesis Does Not Indicate That A POSA Would Have Reasonably Expected Certain Results

Petitioner also argues that the ECOG 1496 results were not unexpected because its authors wrote: "Our study confirmed the hypothesis that rituximab would

be an effective and safe maintenance after CVP chemotherapy." Pet. 60. Petitioner presumes, without evidentiary support, that "the hypothesis" referred to in the JCO article was shared by persons of ordinary skill prior to the time of the invention and not merely the assignee and its collaborators. Moreover, proving and disproving a "hypothesis" has long been part of the vernacular of clinical trial design. Ex. 2054 ¶¶198-200; *see generally* Ex. 2055 (Blackwelder 1982). Using the word "hypothesis" in a clinical report hardly suggests that a person of ordinary skill would have reasonably expected certain results. Ex. 2054 ¶¶198-200.

3. Results Of The Claimed Invention Were Different In Kind Compared To Results Of The Prior Art

As discussed above in Section VI.B, Petitioner's expert acknowledged at deposition that "standard care" for LG-NHL patients was no maintenance therapy because attempts at using chemotherapy and interferon had been "abandoned." This was because no prior-art maintenance regimen had been able to (1) improve progression-free survival with a tolerable toxicity profile, and (2) improve overall survival. *See* Ex. 1029, 1607; Ex. 2057, 002.

Also discussed above in Section VI.B, the invention claimed by the '172 patent changed standard practice. Petitioner's expert acknowledged at deposition that the treatment regimen claimed by the '172 patent has been proven to (1) improve progression-free survival with a tolerable toxicity profile, and (2) improve overall survival. Rituximab maintenance is now standard of care. Ex. 2054 ¶¶201-03. The

results of the claimed invention are different in kind compared to the prior art and support a finding of nonobviousness. *Id*.

VII. UNCONSTITUTIONALITY

Patent owner preserves the argument that this IPR proceeding is unconstitutional under the Due Process Clause because the AIA statute applies to patents issued prior to its enactment, an issue expressly reserved by the Court in *Oil States Energy Services v. Greene's Energy Group*, 138 S. Ct. 1365, 1379 (2018). Patent Owner also preserves the argument that PTAB Judges, when exercising their patent cancellation authority, are principal officers under the Appointment Clause and therefore have not been validly appointed, an issue pending before the Court in *Lucia v. SEC*, No. 17-130, cert. granted, 138 S. Ct. 736 (2018).

VIII. CONCLUSION

Biogen respectfully submits that the Board should reject Petitioner's argument that Claim 1 is unpatentable.

Dated: November 13, 2018

Respectfully submitted,

/s/Michael R. Fleming

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, the undersigned certifies that on November 13, 2018, a copy of the foregoing documents **BIOGEN, INC.'S PATENT OWNER RESPONSE, PATENT OWNER'S EXHIBIT LIST** and **EXHIBITS 2049-2060** have been served in their entireties via electronic mail, as agreed, on counsel of record for petitioner 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 13,992 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, table of exhibits, signature block, certificate of service, or this certificate of word count.

Dated: November 13, 2018

Respectfully submitted,

/s/ *Alaina Bird*
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