UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER INC.,
Petitioner,

v.

BIOGEN, INC.,
Patent Owner.

Case: IPR2018-00285
Patent No. 8,329,172 B2

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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I. INTRODUCTION: THE ’172 PATENT CLAIM IS OBVIOUS

A person of ordinary skill in the art (POSA) would have been motivated to use the clinically tested and only FDA-approved dosing regimen for rituximab as maintenance therapy on LG-NHL patients who responded to CVP induction with a reasonable expectation of successfully extending remission with lower toxicity. The assertions in Patent Owner’s Response (POR) do not change this conclusion.

The standard of care for LG-NHL patients was to forego maintenance therapy after CVP induction therapy due to the intolerable toxicity associated with chemotherapeutic agents and interferon. By the effective filing date, it was well known that rituximab lacked those same toxicities. Rituximab was known to be effective against LG-NHL, and a dosage schedule for LG-NHL patients had been clinically tested and FDA-approved. It was also known that cancerous B-cells would begin to recover 6 months after this regimen, and that LG-NHL was characterized by relapses beginning at 2 years. A POSA would have reasonably expected that the prior art rituximab LG-NHL therapy could be used as a maintenance therapy at the dose and regimen specified in the challenged claim to successfully delay relapse. The secondary considerations alleged by Patent Owner have no nexus to the claim and therefore do not support non-obviousness. Claim 1 of the ’172 patent is obvious.

II. THE PRIOR ART WAS PUBLICLY ACCESSIBLE

All six prior art references raised by the Petition were publicly accessible before the effective filing date. "A reference is considered publicly accessible upon a satisfactory showing [it had] been disseminated or otherwise made available" to POSAs exercising reasonable diligence. *Jazz Pharms., Inc. v. Amneal Pharms., Inc.*, 895 F.3d 1347, 1355-56 (Fed. Cir. 2018). Each reference was shown to be publicly accessible before the effective filing date. *See* Pet., 29-37.

Patent Owner argues that the journals or the articles themselves (presumably Hochster I, Maloney, and McNeil) were not publicly accessible because they were not shown to be cataloged and indexed by libraries. *See* POR, 10. This argument has no legal basis. The articles were published over a year before the effective filing date in established scientific journals. *See* Ex. 1005 (Hochster I), Ex. 1008 (Maloney), Ex. 1003 (McNeil); *see also* Ex. 1016 ¶¶37-39 (corroborating MARC record date with library stamp for the each reference, and verifying each reference issue contained the article). Each of the journal articles and the PDR label were cataloged, indexed, and accessible to the public. Pet., 29-31, 36-37; Ex. 1016 ¶¶37-40. Patent Owner's expert, Dr. Oleksowicz, confirmed that POSAs would have received journals such as Blood (*e.g.*, Maloney, Ex. 1008) and received abstracts disseminated by the American Society of Clinical Oncology before and at

conferences (*e.g.*, Hochster I, Ex. 1005) "to keep abreast of new developments." Ex. 1061, 17:22-18:24, 29:11-30:4, 151:11-17; *see also* Ex. 1060 ¶¶55, 58, 64, 70.

Patent Owner's reliance on *Acceleration Bay* and *Bayer* is misplaced, since the references in those cases were not widely disseminated in scientific journals and there was evidence that the references were not publicly disseminated or sufficiently indexed or cataloged. *See Acceleration Bay v. Activision Blizzard*, 908 F.3d 765, 773 (Fed. Cir. 2018) (reference only available to certain personnel, and search form was deficient); *In re Bayer*, 568 F.2d 1357, 1362 (C.C.P.A. 1978) (thesis only available to graduate committee). If accessibility is proven, there is no requirement to show that particular members of the public actually received the information. *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1569 (Fed. Cir. 1988). MARC records indexing and cataloging the journal references across libraries and Dr. Hall-Ellis' testimony concerning library practices sufficiently establishes that these references would have been shelved and available within days of each reference's MARC record creation. *See* Pet., 29-31, 36-37; *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986) ("general library practice may be relied upon to establish an approximate time when a thesis became accessible"). "[T]he realities of routine business practice counsel against requiring" "evidence establishing a *specific* date of cataloging and shelving before the critical date." *Id.* Additionally, Petitioner's expert Dr. Soiffer confirmed that

POSAs had access to these references, including by direct dissemination or through libraries (Ex. 1060 ¶¶55, 58, 64, 70), and Dr. Oleksowicz did not dispute their availability. *See* POR, 9-12 (failing to cite Ex. 2054).

Patent Owner does not explain the accessibility challenges to the FDA and Website labels in its POR. Instead it improperly attempts to incorporate by reference challenges from another proceeding. *See* POR, 11-12, referencing challenges raised in Prelim. Resp. of IPR2017-01166 addressed by Ex. 2044; 37 C.F.R. §§ 42.6(a)(3), 42.24(b)(2); *see also Brunswick Corp. v. Cobalt Boats, LLC*, IPR2015-01060, Paper No. 78, at 39 (rejecting "maintains its position" as "improper incorporation by reference"). This Board already considered those challenges and found the Petition addressed those concerns. *See* Decision, 21; Pet., 31-36. Patent Owner's expert testified that she prescribed rituximab within several months of its November 1997 FDA approval, and that it was her practice to be familiar with contents of a drug's FDA label before prescribing it. *See* Ex. 1061, 21:4-11, 21-24, 24:20-25:5, 10-14; *see also* Pet., 35; Ex. 1060 ¶62; Ex. 1062 (Soiffer Reply Decl.) ¶5. Petitioner also served supplemental evidence under 37 C.F.R. § 42.64(b)(2) of a declaration from Christopher Butler of the Internet Archive, authenticating and verifying the date of availability of the Website label and search feature available for a POSA to find the Website label. *See* Ex. 1059;

IBM v. Intellectual Ventures II, IPR2015-00089, Paper No. 44, 53-54 (PTAB Apr. 25, 2016); Ex. 1060 ¶63.

Finally, Patent Owner challenges public accessibility of the ECOG 1496 protocol, which is not an exhibit, basis for ground, or at issue in this proceeding. *See* Ex. 2051, 97:23-98:2 (testifying he did not cite the protocol). While a POSA would have known of the E1496 study (disclosed by Hochster I, Ex. 1005, 9; Ex. 2054, 182:1-25) and that the study had a protocol (Ex. 2051, 98:3-13), Patent Owner does not cite or rely on the contents of the protocol.

III. CLAIM 1 IS OBVIOUS IN LIGHT OF THE PRIOR ART

A. Hochster I Discloses Patients Responding to CVP Therapy

The Board construed claim 1 to require that "CVP therapy must be followed at some time by the rituximab maintenance therapy, with no disease relapse occurring between the patient's response to the CVP therapy and the maintenance therapy." Decision, 7. Petitioner and Dr. Soiffer applied this construction. Pet., 18; Ex. 1060 ¶¶27-28. Hochster I discloses a study of CVP induction therapy followed by a plan for maintenance rituximab therapy, which a POSA would understand to be administered to responders. Pet., 39-41; Ex. 2054 ¶153.

Dr. Oleksowicz agreed that a POSA would define maintenance therapy in the context of responders: "Therapies designed to prevent relapse ***in patients who respond to induction therapy*** are called 'maintenance' therapies." Ex. 2054 ¶31

(emphasis added); *see also* Ex. 1060 ¶80. Despite this agreement, Dr. Oleksowicz opined that maintenance therapy could also be given to non-responders. Ex. 2054 ¶77. Even if maintenance therapy was also administered to non-responders in the prior art, claim 1 would still be obvious. A POSA would have been motivated to treat an LG-NHL patient who has responded to CVP induction with the clinically tested and FDA-approved dosage as rituximab maintenance therapy and have a reasonable expectation of success that the treatment would be effective. Ex. 1060 ¶¶87-90, 111. In addition, a POSA would have understood that giving maintenance therapy to non-responders was uncommon. Ex. 1062 ¶6. Unless informed otherwise, a POSA would not have understood that maintenance therapy was given to non-responders. *Id.* Hochster I does not disclose administering anti-CD20 maintenance to patients with stable disease. *Id.* ¶¶6, 10.

Patent Owner argues that "CVP therapy to which a patient responds" is not found in the cited art unless the reference recites the specific definition for responders disclosed in the '172 patent. This argument fails. The claim term "to which a patient responds" and the disclosure of "complete response," "partial response," and "non-responders" (*see* Ex. 1001, 9:14-23) reflect nothing more than the common understanding a POSA would have of a "responder" to a treatment. The '172 patent demonstrates this when it later discloses that "*[r]esponders* [to CVP] … will undergo Rituximab maintenance therapy …." *Id.* at 13:10-16

(emphasis added). The latter passage uses the term "responder" generally without referring to the specific criteria set forth at 9:14-23. *See* Ex. 1062 ¶8. Although the specific criteria defining complete and partial responders might differ between studies, a POSA would have understood that "responders" in a study meets the term "to which a patient responds" in the claim. *Id*. at ¶¶7-8; Ex. 2054 ¶35

Consistent with this position, Dr. Oleksowicz testified that the '172 patent defines responders not for CVP therapy or patients receiving maintenance rituximab, but rather for rituximab induction therapy. *See* Ex. 1001, 9:1-13; Ex. 1061, 86:5-18, 87:1-12; *see also* Ex. 1062 ¶8; Ex. 1061, 142:18-143:7 (admitting that the results of the ECOG 1496 study disclosed by Hochster I were applicable despite using a different definition of responders from the '172 patent). Dr. Oleksowicz's testimony further supports the position that determining whether a patient has responded to CVP therapy must be done by the understanding known and used in the prior art by a POSA. Ex. 2054 ¶35 (stating that her "opinions would remain the same if claims terms are construed given their ordinary or customary meaning to a person skilled in the art as of the relevant time"); *see also* Ex. 1061, 66:24-67:2. Thus, this is not a difference between the claim and the prior art and is not pertinent to an obviousness analysis. *See Merck & Co. v. Teva Pharms.*, 395 F.3d 1364, 1374 (Fed. Cir. 2005) (error to distinguish prior art where the claimed invention "adds nothing beyond the teachings" of the prior art).

Patent Owner's reliance on *Medtronic* and *Elbit* is misplaced. In *Medtronic*, the prior art did not disclose the specific procedures recited in the claim, nor were they common knowledge to a POSA. *Medtronic, Inc. v. Barry*, 891 F.3d 1368, 1376-77 (Fed. Cir. 2018). Similarly, in *Elbit* the claims required a two-step process not explicitly taught in the prior art reference nor within the general knowledge of a POSA. *Elbit Sys. v. Thales Visionix, Inc.*, 881 F.3d 1354, 1357, 1359 (Fed. Cir. 2018). Here, CVP was a well-known induction therapy for LG-NHL patients that successfully induced responses in LG-NHL patients. *See* Ex. 1001, 13:10; Ex. 2054 ¶29; *see also id.* at ¶27; Ex. 1061, 100:23-101:5; Ex. 1060 ¶76; Pet., 40. The claims here only require standard CVP therapy that induced known responses in LG-NHL patients in combination with the clinically tested and only FDA-approved dosing regimen in the prior art for rituximab. *See* Ex. 1061, 93:14-21, 94:7-18.

Hochster I discloses a study of CF induction therapy in LG-NHL patients where the "[r]esponse rate was 100%." Ex. 1005, 9; Ex. 1062 ¶9. "Based on these promising results," Hochster I discloses comparing CF and CVP induction therapies. Ex. 1005, 9; Ex. 1062 ¶10; Ex. 1060 ¶78. A POSA would have understood that the CVP induction therapy disclosed by Hochster I would induce responses in LG-NHL patients, and that one of the purposes of the follow-on study disclosed was to compare CF and CVP induction therapies and to test anti-CD20

maintenance therapy in responders to those induction therapies. Ex. 1062 ¶¶6, 10. A POSA would have understood the CVP induction therapy referenced by Hochster I would induce responders who do not materially differ from the criteria in the '172 patent. Ex. 1062 ¶¶7-8; Ex. 2054 ¶35.

B. POSAs Would Have Been Motivated to Use Rituximab for Maintenance Therapy

A POSA would have been motivated to use the clinically tested and FDA-approved rituximab dosage regimen for LG-NHL patients as maintenance therapy. *See* Ex. 1060 ¶¶85, 93, 107, 109; Ex. 2054 ¶153. Patent Owner's expert admits that the reason no maintenance was the standard of care for LG-NHL patients was previous chemotherapy and interferon maintenance treatments had "intolerable" toxicity. Ex. 2054 ¶158; *see also* Ex. 1060 ¶49. The prior art clinically-tested and FDA-approved rituximab dosing regimen presented an obvious maintenance therapy that lacked the same toxicities. Ex. 1060 ¶¶98, 109; Ex. 1062 ¶20. Patent Owner's expert conceded that "[i]n general, Rituxan is a tolerable drug." Ex. 1061, 49:25. Reasons to avoid chemotherapy and interferon maintenance did not apply to rituximab. Ex. 1062 ¶¶19-20.

A POSA would have been motivated to use rituximab as a maintenance therapy for patients who responded to CVP induction therapy. Ex. 1005, 9; Ex. 1060 ¶93. That rituximab was approved only as an induction therapy at the time does not affect this motivation. LG-NHL patients were expected to relapse with

the passage of time and succumb to the disease. Ex. 2054 ¶27. The primary reason previous maintenance therapies were not administered was because of their extreme toxicity reducing patients' quality of life. *See* Ex. 1060 ¶¶46, 49. A POSA would have been motivated to provide the less toxic, safe rituximab dosing regimen as maintenance therapy and have a reasonable expectation that it would be well tolerated and effective. Ex. 1060 ¶¶89-90, 93, 107, 111.

Patent Owner's argument that a POSA would not deviate from standard of care treatment is inconsistent with the prior art and the law. *Compare KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (POSA "is also a person of ordinary creativity, not an automaton") *with* Ex. 1061, 12:8-13:24 (repeatedly stating a POSA would have strictly followed the standard of care). In evaluating whether patent claims are obvious, it is proper to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ," especially when exploring a "finite number" of solutions. *Yeda Research & Dev. Co. v. Mylan Pharms., Inc.*, 906 F.3d 1031, 1048 (Fed. Cir. 2018) (obvious to select three days out of a week for drug dosing); Ex. 1060 ¶85.

In view of Hochster I's disclosure of anti-CD20 maintenance, a POSA would have found it obvious to try rituximab as one of a finite number of solutions. Ex. 1060 ¶85; Ex. 1005, 9; Ex. 2054 ¶153 (acknowledging Hochster I discloses a "plan to study rituximab maintenance in LG-NHL"). Patent Owner's expert

conceded there were only two known anti-CD20 drugs at the time other than rituximab: Bexxar and Zevalin. Ex. 1061, 39:15-21; *see also* Ex. 1062 ¶11. In addition to anti-CD20 therapy, Bexxar and Zevalin also provide radiotherapy, which entails additional toxicities over rituximab. Ex. 1062 ¶11; Ex. 1008, 1. These alternatives are also not chimeric human antibodies, and are more likely to induce autoimmune responses. Ex. 1062 ¶11; Ex. 2039, 8. Hochster I is silent on radiotherapy, so a POSA would have reasonably concluded that it refers to rituximab. Ex. 1062 ¶12; *see also* Ex. 2054 ¶153. Thus, a POSA would have understood Hochster I to disclose rituximab of three possible choices, and given the known tolerability of rituximab and its FDA approval, a POSA would have had good reason to pursue maintenance rituximab over the other two possible choices. Ex. 1060 ¶¶52, 88-89, 93-94, 107, 111; Ex. 1062 ¶11; *KSR*, 550 U.S. at 421 (patent invalid as obvious if "there are a finite number of identified, predictable solutions, [and] a person of ordinary skill has good reason to pursue the known options within his or her technical grasp").

A POSA would also have been motivated to use rituximab as a maintenance therapy because of the successful use of rituximab in non-maintenance treatments (*e.g.*, monotherapy on relapsed LG-NHL patients). Ex. 1062 ¶13. For example, the authors of the van Oers publication decided in 1998 to launch a trial "to establish the effect of maintenance treatment with rituximab on progression-free

survival" based on "the efficacy of rituximab monotherapy in relapsed low-grade lymphoma," among other reasons. *Id.*; Ex. 2013, 2; *see Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003) (approving "later publications as evidence of the state of art existing on the filing date of an application."). A POSA would not have ignored an effective, approved drug for induction therapy as an option for maintenance therapy. Ex. 1062 ¶13; *see also* Ex. 1060 ¶53; Ex. 1008, 12.

C. Hochster I and Maloney Disclose Administering Maintenance Rituximab in Four Weekly Doses of 375 mg/m^2

The clinically tested and approved dosage regimen for rituximab was four weekly doses at 375 mg/m^2. Ex. 1008, 6. It was known to be safe and efficacious for LG-NHL. Ex. 1060 ¶¶59, 92; Ex. 1008, 6-7. It would have been obvious to select this dosage regimen based on the clinical data provided in Maloney demonstrating its effectiveness as an anti-CD20 treatment and favorable safety profile in LG-NHL patients. Pet., 44-46.

Maloney disclosed a range of possible dosage regimens, including four weekly doses of 125 to 375 mg/m^2. Pet., 47-48; Ex. 1060 ¶95, Ex. 1008, 7. Since the disclosed ranges include the claimed dosage regimen, Patent Owner had the burden of coming forward with evidence to rebut the presumption of disclosure in the art. *See Galderma Labs. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013). Patent Owner failed to identify evidence in response to this burden. POR, 31-32.

While Maloney tested four weekly doses of 375 mg/m^2 in relapsed or refractory LG-NHL patients, a POSA would not have altered the regimen when administering maintenance rituximab. Ex. 1060 ¶¶97-99. Maloney discloses additional alternatives, but did not warn or teach against this dose. *Id.* ¶97. *See SightSound Techs., LLC v. Apple Inc.*, 809 F.3d 1307, 1320 (Fed. Cir. 2015) (disclosure of alternatives without discouraging the claimed solution does not teach away from it).

Patent Owner identified CVP and interferon maintenance regimens as examples that would offer guidance in lower-dose maintenance regimens. Ex. 2054 ¶¶158, 166-168. These are highly toxic drugs. A POSA would not have been influenced by the dosing of different highly toxic drugs to limit a rituximab maintenance regimen to a dose lower than the well-tolerated, safe, approved dose. Ex. 1060 ¶¶52, 98, 109. A POSA would also not have been motivated to reduce the dosage simply because the tested and approved dose was specified for relapsed or refractory patients who may have been more resistant. *Id.*; *see also* EX2051, 45:16-19. Maloney established that there was no "dose limiting toxicity" for four weekly doses up to 375 mg/m^2, so there were no toxicity concerns with the dosage regimen recommended by Maloney. Ex. 1060 ¶¶52, 98; Ex. 1008, 7; *see also* Ex. 1061, 49:25 ("In general, Rituxan is a tolerable drug").

Maloney also determined that the regimen of four weekly doses at 375 mg/m^2 had a favorable "safety profile." Ex. 1060 ¶59; Ex. 1008, 6. A POSA would therefore not have been motivated to reduce this dosage regimen that Maloney established to be safe and of tolerable toxicity. *See also* Ex. 2051, 45:16-19. While Grossbard characterizes the fact that "a maximum tolerated dose" for rituximab had not been established as a "stumbling block" to determining the optimal dose, this is not in the context of maintenance therapy and does not caution against using a clinically tested, FDA approved, safe and effective dose. *See* POR, 18, citing Ex. 2039, 10. Notably, Patent Owner disagreed with this characterization during prosecution of the '172 patent, arguing that the optimal dose for rituximab induction therapy had been established in the prior art. Ex. 1022, 16. Dr. Soiffer also disagreed with Grossbard's characterization because effective therapies were known, as Maloney had established. Ex. 2051, 178:19-180:17.

The McNeil reference would also not have motivated a POSA to alter the clinically tested and approved rituximab dosing regimen. Patent Owner argues that McNeil discloses single doses of rituximab maintenance therapy in IG-NHL patients (*see* POR, 17, based on a hypothetical concerning an extended induction therapy with no mention of responders or maintenance), but admits that McNeil fails to define the dose. Ex. 1003, 5; Ex. 1060 ¶100. McNeil therefore does not

motivate or teach changing the dosing amount. Ex. 1062 ¶14; Ex. 1061, 117:21-118:3. As discussed above, Maloney provides a clear dosage regimen for LG-NHL supplying the information a POSA would seek. Ex. 1060 ¶¶91-99.

Patent Owner also argues that, generally, maintenance therapies are less intensive than induction therapies because responders generally have less tumor burden. *See* POR, 3-4, 21-23, 26-27, and 29. Patent Owner offers no evidence linking tumor burden to dosage, particularly in the context of maintenance therapy. While some evidence links tumor burden as inversely proportional to rituximab serum levels (POR, 23-24, 25-26), in the context of maintenance therapy, a POSA would have been interested in safely maintaining rituximab serum levels in line with expected B cell recovery times. *See* Ex. 1060 ¶111; Ex. 2051, 116:20-119:11; *see also* Section III.E below. Responders may vary in terms of tumor burden, and partial responders might have more tumor burden than some non-responders with stable disease. Ex. 1061, 126:12-21; Ex. 2051, 54:23-56:1. Tumor burden also varies for patients receiving induction therapies, yet induction therapy dosage regimens do not take this into account. Ex. 1062 ¶20. Patent Owner provided no evidence that concerns over tumor burden would affect a POSA's motivation to adopt the dosage regimen disclosed by Maloney.

D. Hochster I and the Rituxan™ Labels Disclose Administering Rituximab Maintenance in Four Weekly Doses of 375 mg/m^2

Hochster I discloses administering "anti-CD20 maintenance" to responders to CVP induction therapy, and rituximab was only one of a few anti-CD20 maintenance treatments known as of August 1999. *See* Sections A-B above; Pet., 40-41. Indeed, rituximab was the only anti-CD20 agent that had been approved by the FDA (Ex. 1060 ¶109), and the only FDA-approved dosage regimen was four weekly doses at 375 mg/m^2. *Id.*; Ex. 1004, 2; Ex. 1039, 12; Ex. 1041, 3.

Patent Owner's distinction of *Pfizer* misses the point. In *Pfizer*, the POSA "looked to pharmacopoeias and compendia to find a salt that was previously approved by the FDA and used successfully within the pharmaceutical industry." *Pfizer v. Apotex*, 480 F.3d 1348, 1366 (Fed. Cir. 2007). The Court found it would be logical to try the 53 listed FDA-approved salts. *Id.* at 1362. Here, there is one known FDA-approved rituximab dosage schedule to treat LG-NHL. Unlike in *Lilly* and *Am. Hosp.*, a POSA would have found it obvious to use this rituximab dosage schedule to treat patients with the same disease. *See Eli Lilly & Co. v. Teva Pharms.*, 619 F.3d 1329, 1337 (Fed. Cir. 2010) (rejecting application of autoimmune treatment to postmenopausal osteoporosis with no credible connection between the two diseases); *Am. Hosp. Supply Corp. v. Travenol Labs., Inc.*, 745 F.2d 1, 7 (Fed. Cir. 1984) (distinguishing prior art directed to general nutritional support from claim limited to liver disease). It would have been obvious and most

efficient for a POSA to select this dosage regimen based on its FDA-approval, its effectiveness as an anti-CD20 treatment, and favorable safety profile in LG-NHL patients. Pet., 52-54.

While the FDA-approved indication was for relapsed or refractory LG-NHL patients (POR, 26), a POSA would not have altered the regimen when administering maintenance rituximab for the same reasons a POSA would not have changed the dosage disclosed by Maloney as explained above. *See* Section III.C above. Ex. 1062 ¶20.

E. McNeil Discloses Administering Maintenance Rituximab Every Six Months for Two Years

McNeil describes a trial for maintenance rituximab administered every six months for two years in elderly IG-NHL patients who responded to initial CHOP therapy. Ex. 1003, 5. CHOP includes doxorubicin, which has synergies with rituximab, theoretically permitting a lower dose. Ex. 1062 ¶14. However, McNeil does not disclose a rituximab dosage amount and therefore provides no reference for changing that amount. Ex. 1061, 116:3-24; Ex. 1062 ¶14.

A POSA would have understood from McNeil that the frequency and duration of its maintenance treatment was acceptable for an elderly population, even though it would have prolonged B-cell suppression. Ex. 1062 ¶15. A POSA would also have understood that an elderly population was more susceptible to toxicities than a general population including younger people. *See* Ex. 1061,

61:11-20; Ex. 1062 ¶15. A POSA would have concluded that the frequency and duration of treatment disclosed by McNeil would likely be safe for a general population. Ex. 1062 ¶15. There was no "tremendous safety risk" of long-term B-cell suppression notwithstanding a patient population more susceptible to toxicities. *Cf.* POR, 48; *see also* Ex. 2039, 10 ("no major toxicity has been seen with rituximab, despite prolonged B-cell depletion following therapy"). A POSA concerned about toxicity or prolonged B-cell suppression would have understood that LG-NHL was a fatal disease, so some degree of toxicity and B-cell suppression of B-cells would be acceptable. Ex. 1062 ¶15. It would have been obvious for a POSA to use the frequency and duration disclosed by McNeil in a maintenance rituximab dosing regimen as of August 1999. Ex. 1060 ¶101.

Patent Owner asserts that the outcome an IG-NHL treatment regimen does not predict the efficacy of that treatment against LG-NHL. *See* POR, 36; Ex. 2054 ¶114. A POSA would nevertheless find information from an IG-NHL study relevant to a maintenance regimen for LG-NHL patients. Ex. 1062 ¶16. A POSA would have knowledge extending to all NHL, and would not have ignored data from non-LG-NHL treatments, particularly data for the same drug and therapy (i.e. rituximab maintenance). *See* POR, 12 (POSA would have "experience treating NHL patients"); Ex. 1061, 22:15-21 ("NHL encompasses all types, including…

intermediate-grade and low-grade non-Hodgkin's lymphoma"); *see also* Ex. 1062 ¶16.

A POSA also would have been motivated to follow the maintenance frequency disclosed by McNeil based on the nature of LG-NHL. LG-NHL patients generally have only two to three years of relapse-free survival following induction. Ex. 1061, 105:2-23; Ex. 2054 ¶27. A POSA would have found it obvious to conduct maintenance therapy following induction for two years. Ex. 1062 ¶17.

In addition, to maintain the suppression of cancerous B-cells, a POSA would have been motivated to prescribe maintenance treatments every six months. Ex. 1060 ¶102. Patent Owner's expert agreed that McLaughlin "showed B cell levels were similarly suppressed at three and six months" after rituximab treatment. Ex. 2054 ¶143; Ex. 1006, 8. Maloney further disclosed that suppressed B-cells were "nearly undetectable until approximately 6 months post-treatment," at the beginning of a "slow gradual recovery." Ex. 1008, 9; Ex. 1060 ¶102. This is consistent with the disclosure of B-cell recovery beginning at "approximately six months following completion of treatment" on the Rituxan™ label. Ex. 1004, 2; Ex. 1039, 11; Ex. 1041, 1.

Even if a POSA might also have considered administering treatments every three months, that is simply an alternative and nothing in the art taught against six month treatment intervals. *See SightSound*, 809 F.3d at 1320. As the experts

agreed, McLaughlin indicated that treatments were similarly effective at three and six months. Ex. 2054 ¶143. A POSA would have preferred the six month interval disclosed by McNeil as more likely to be safe for a general population. Ex. 1062 ¶15.

F. POSAs Would Have Had a Reasonable Expectation of Success

A POSA would have a reasonable expectation that a treatment plan based on Hochster I, in view of Maloney or any of the Rituxan™ label references, and McNeil, would successfully prolong relapses in LG-NHL patients. Pet., 38-39, 42, 44, 49, 57, 62.

While the medicinal arts may be unpredictable, "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Allergan, Inc. v. Sandoz, Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013). Hochster I disclosed a Phase III trial—an advanced phase of study based on promising results in humans. It was not a "bare proposal" based only on animal studies as in *Eli Lilly*. *See* POR, 49, citing *Lilly*, 619 F.3d at 1338. Phase III studies cost tens of millions of dollars, so companies "will not rush into a Phase III comparative study unless they think there is a very high likelihood or likelihood that they will be successful." Ex. 2051, 81:1-82:3, 82:15-23. That Phase III studies may fail does not mean that success could not be

reasonably expected; "[c]onclusive proof of efficacy is not necessary." *Hoffman La Roche, Inc. v. Apotex, Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014).

Patent Owner speculates that antigen escape might have sowed doubt in a POSA, but Dr. Soiffer testified that a POSA would not be concerned that antigen escape would impact the reasonable likelihood of success, since "antigen escape is going to occur more frequently in individuals that have a higher tumor burden," while responders receiving maintenance therapy generally have lower tumor burden. Ex. 2051, 79:6-80:22; Ex. 2054 ¶97.

That Hochster I did not disclose results does not distinguish it from the '172 patent, which also did not report any results. The lack of results therefore cannot be considered as part of the obviousness analysis. *See Merck*, 395 F.3d at 1374. As Dr. Soiffer testified, a Phase III trial, like that described by Hochster I, demonstrated that companies comprised of POSAs in this field reasonably expected success, not merely a possibility. *Compare* Ex. 2051, 81:1-82:3, 82:15-23 *with* POR, 48-49.

Hochster I specifically disclosed "anti-CD20" maintenance. The only FDA-approved anti-CD20 treatment that had been extensively clinically studied at the time was rituximab. There was a clear dosage regimen shown to be effective, safe, and tolerable in LG-NHL patients. This is not a situation where a POSA would have to "vary all parameters or try each of numerous possible choices until one

possibly arrived at a successful result." *See* POR, 48-50, citing *Medichem v. Rolabo*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) and *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Unlike in *Medichem*, the prior art here disclosed the claimed dosage regimen.

Chemotherapy and interferon maintenance (which were known to prolong progression-free survival, *see* Ex. 1060 ¶¶44, 46-49) do not refute the reasonable expectation of success because they do not fall within the claim. Patent Owner's case, *Cyclobenzaprine*, holds that only failures "to develop ***a claimed invention***" negate an expectation of success. *See In re Cyclobenzaprine*, 676 F.3d 1063, 1081 (Fed. Cir. 2012) (emphasis added). Rituximab was known to lack those toxicity issues, so it would have been reasonable for a POSA to expect rituximab to succeed as maintenance therapy.

IV. OBJECTIVE INDICIA DO NOT SUPPORT NON-OBVIOUSNESS

Patent Owner has not shown a nexus between the asserted objective indicia and "what is both claimed and *novel*," and therefore its indicia should be accorded no weight. *Novartis AG v. Torren Pharms.*, 853 F.3d 1316, 1330 (Fed. Cir. 2017). Patent Owner has not shown unexpected results tied to the specific dosage limitations of claim 1, separate from the properties of rituximab itself. The objective indicia referenced by Patent Owner do not overcome Petitioner's *prima facie* showing of invalidity.

A. No Long Felt But Unmet Need

Patent Owner asserts there was a long felt but unmet need for "maintenance that was effective and had tolerable toxicity." POR, 56. Even if these features were claimed, it was well established that rituximab had a tolerable toxicity profile and was effective in LG-NHL patients (*see* Sections III.C-D above) long before the patent application was filed. Previous maintenance therapies were known to prolong progression-free survival effectively even though they had intolerable effects. *See* Ex. 1060 ¶¶44, 46-49.

Patent Owner relies on the results of the ECOG 1496 study, but never attempted to show a nexus between that study and the claim. *See* POR, 56-59. Dr. Oleksowicz admitted that the ECOG 1496 study used different criteria for responders than that specified by the '172 patent. Ex. 1061, 140:1-141:20. Though she opined those differences were minor, she never compared the other limitations of the claim to the ECOG 1496 study. *Id.* at 142:18-143:7.

Even assuming a nexus between the ECOG 1496 study and the claim, the study acknowledges that it was unable to show longer overall survival. Ex. 2054 ¶193. Patent Owner relies on a "meta-analysis" combining numerous studies to show an improvement in overall survival, but Dr. Oleksowicz admitted that those studies used various therapies not covered by the '172 patent and therefore there is

no nexus between that meta-analysis and the claim. Ex. 1061, 135:10-24; Ex. 2051, 229:8-230:19.

The ECOG 1496 study also refers to numerous other studies of treatments falling outside the claim that achieved similar results. *See* Ex. 1029, 5-6; Ex. 1061, 130:12-131:6 (admitting the same result achieved with unclaimed induction therapies). For example, one study (reference 14) showed longer progression-free survival (PFS) in patients receiving rituximab and CHOP induction therapy (unclaimed) and one 375 mg/m^2 maintenance rituximab dose every three months (also unclaimed). Ex. 1029, 6; *see also* Ex. 2013, 1; Ex. 1060 ¶¶44, 46-49. These studies show the claimed dosage schedule was not required to achieve similar results.

B. No Unexpected Results

Patent Owner alleges the ECOG 1496 study demonstrates the unexpected success of the claimed invention. Here, too, Patent Owner argues that increased survival with minimal toxicity was unexpected. Yet the ECOG 1496 study did not show increased overall survival and it was already known that rituximab was less toxic. *See* Ex. 1061, 140:1-141:20; Ex. 2054 ¶193. The meta-analysis Patent Owner relies on did not cover therapies claimed by the '172 patent. Ex. 1061, 135:10-24. The increases in progression-free survival were seen in numerous studies testing therapies that fell outside the claim as well. *See* Ex. 1029, 5-6; Ex.

1061, 130:12-131:6; Ex. 2013, 1; *see also* Ex. 1060 ¶¶44, 46-49. Since these results were obtainable by numerous unclaimed dosage regimens, Patent Owner has not shown that the claimed dosage schedule has a nexus with these results.

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Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH 37 CFR 42.24(c)(1)

1. This brief complies with the type-volume limitation of 37 CFR 42.24(c)(1) because:

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Petitioner's Reply to Patent Owner's Response was served on January 24, 2019, by filing this document through Patent Trial and Appeal Board End to End system as well as delivering a copy via electronic mail upon the following attorneys of record for Patent Owner Biogen, Inc.:

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