Paper No. __

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Boehringer Ingelheim International GmbH and
Boehringer Ingelheim Pharmaceuticals, Inc.,
Petitioners,

v.

Biogen Idec, Inc.,
Patent Owner.

Case IPR2015-00418
Patent 8,329,172 B2

PETITIONERS' REQUEST FOR REHEARING ON THE INSTITUTION DECISION UNDER 37 C.F.R. § 42.71(d)

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page

CASES

REGULATION

I. INTRODUCTION AND STATEMENT OF RELIEF REQUESTED

Petitioners respectfully request the Board grant rehearing to reconsider its Decision (Paper No. 14) declining to institute *inter partes* review of U.S. Patent No. 8,329,172 ("the '172 patent") on one of the grounds raised in the petition: the combination of McLaughlin (Ex. 1009) and McNeil (Ex. 1005). Due to Patent Owner's mischaracterizations in its Preliminary Response (Paper No. 11), the Board misapprehended the teachings of the prior art, as presented in the Petition (Paper No. 1), in determining that:

(i) administering rituximab maintenance therapy is different from treating minimal residual disease ("MRD");

(ii) an alleged synergy between rituximab and the doxorubicin component of the CHOP chemotherapy regimen would have prevented a skilled artisan from using CVP induction therapy (*i.e.*, CHOP without doxorubicin); and

(iii) McNeil's teachings somehow discouraged the use of less toxic alternatives to CHOP other than "mini-CHOP."

In particular, the Patent Owner led the Board to incorrectly find that McLaughlin in view of McNeil does not teach or suggest to an ordinary artisan that rituximab can be used as a maintenance therapy because there is a "difference" between treating MRD and maintenance therapy—a factual finding flatly contradicted by the record evidence. The Board also incorrectly concluded that the

use of CVP chemotherapy would not have been obvious based on the teachings of McLaughlin and McNeil. For the reasons set forth below, the Board should grant rehearing and institute *inter partes* review based on the combination of McLaughlin and McNeil.

II. STANDARD OF REVIEW

A request for rehearing "must specifically identify all matters the party believes the Board misapprehended or overlooked, and the place where each matter was previously addressed in a motion, an opposition, or a reply." 37 C.F.R. § 42.71(d). "When rehearing a decision on petition, a panel will review the decision for an abuse of discretion." 37 C.F.R. § 42.71(c). An abuse of discretion occurs when a decision is "based upon clearly erroneous findings of fact or a misapplication or misinterpretation of applicable law or . . . a clear error of judgment." *PPG Indus. Inc. v. Celanese Polymer Specialties Co. Inc.*, 840 F.2d 1565, 1572 (Fed. Cir. 1988).

III. ARGUMENT

A. Contrary to Patent Owner's Assertions, a Skilled Artisan Would Not Have Distinguished Between Treating Minimal Residual Disease and Maintenance Therapy

As the Decision acknowledges, McLaughlin expressly discloses that "[w]ith its established efficacy in the setting of measurable disease, ***the use of [rituximab] in a minimal or subclinical disease setting is a consideration***" when treating low grade non-Hodgkin's lymphoma ("LG-NHL") patients. Decision at 29 (quoting

Ex. 1009 at 2831) (emphasis added). Nonetheless, Patent Owner asserted in its Preliminary Response that "a person of ordinary skill would have understood that treating minimal residual disease is not maintenance therapy," and that "Dr. Grossbard in his own publications has used the terms 'minimal disease' and 'maintenance therapy' as describing different treatment settings." Prelim. Resp. at 13. The Board adopted Patent Owner's assertions as part of its decision not to institute review based on the combination of McLaughlin and McNeil. Specifically, the Board found that a skilled artisan would not view McLaughlin as teaching the use of rituximab for maintenance therapy in LG-NHL patients because "Patent Owner advance[d] evidence (Prelim. Resp. 51) that ordinary artisans, as well as Dr. Grossbard, recognized a difference between treating minimal disease and using an agent in maintenance therapy . . . ." *See* Decision at 29; *see also id.* at 33.

The Board's decision not to institute trial because of a purported difference that exists between maintenance therapy and treating MRD was based on clearly erroneous findings of fact. Indeed, the Petition, Dr. Grossbard's declaration, and the exhibits of record all demonstrate that the claimed "maintenance therapy" was recognized in the art as a ***way of treating*** MRD.

1. McLaughlin Discloses the Use of Rituximab as a Treatment for Minimal Residual Disease

The Petition highlights the relevant disclosure in McLaughlin that

encouraged the use of rituximab to treat MRD:

> Indeed, McLaughlin explicitly encourages the use of rituximab maintenance therapy in a CR [complete response] (minimal residual disease or MRD) setting following chemotherapy induction when it states that "[w]ith its established efficacy in the setting of measurable disease, the use of this agent in a ***minimal or subclinical disease*** setting is a consideration."

Pet. at 27 (quoting Ex. 1009 at 2831) (emphasis added).

The Petition explains that the "minimal or subclinical disease" mentioned in McLaughlin includes "***residual disease remaining after chemotherapy*** in LG-NHL patients." *Id.* at 39 (emphasis added). Indeed, "even the most aggressive induction therapy le[aves] behind ***residual malignant B-cells*** that would inevitably start growing again, leading to relapse." *Id.* at 32 (citing Ex. 1002 ¶ 57) (emphasis added); *see also* Ex. 1002 ¶¶ 46, 76-77 (recognizing that LG-NHL patients who achieve a complete or partial response after chemotherapy still have MRD remaining). On this point, Petitioners' expert, Dr. Grossbard, testified that a complete response to chemotherapy or complete remission occurs when the "patient has only ***minimal residual disease ('MRD') remaining***." Ex. 1002 ¶ 29 (emphasis added). Importantly, to prevent relapse, oncologists use "***maintenance therapy to treat the residual disease*** remaining after chemotherapy ha[s] driven LG-NHL into a complete or partial remission." Pet. at 33 (citing Ex. 1002 ¶¶ 62-

64) (emphasis added).

According to Dr. Grossbard, "[o]ncologists knew prior to August 1998 that even when a patient with LG-NHL achieved CR based on pre-established criteria, the patient would not be 'cancer-free' ***but rather in a state of minimal residual disease ('MRD')***, which meant that millions or even billions of cancerous B cells could still be present." Ex. 1002 ¶ 57 (emphasis added). Dr. Grossbard explained how maintenance therapy treats MRD:

> As noted above, maintenance therapy or "maintenance" is an extended period of treatment following successful induction therapy. This means that before maintenance therapy is commenced, the patient has already achieved at least some level of reduction in tumor burden, typically a CR or PR [complete or partial response] (based on pre-established criteria). ***Maintenance therapy is intended to treat the residual disease*** to prevent it from being reestablished and thus prevent a deterioration of that "improved" condition of CR or PR.

Id. at ¶ 62 (emphasis added).

In sum, the evidence of record establishes that there is no genuine dispute that (i) at least patients experiencing a complete response (CR) necessarily have MRD; and (ii) maintenance therapy is intended to treat MRD following chemotherapy in order to prevent relapse. By disclosing the use of rituximab to treat MRD as a "consideration" for a person of ordinary skill, McLaughlin also teaches and encourages the use of rituximab as a maintenance therapy. This is

confirmed by other evidence of record demonstrating that maintenance therapy may be used to treat MRD. *See* Ex. 1038 at 8 ("Potentially, the agent could be used singly, in combination with standard chemotherapy, or ***following*** s***tandard chemotherapy in an attempt to decrease minimal residual lymphoma*** and extend the duration of remission.") (emphasis added).

2. Dr. Grossbard Has Never "Recognized a Difference" Between Treating MRD and Maintenance Therapy, as Patent Owner Contends

In denying institution, the Board relied on Patent Owner's argument that Dr. Grossbard, through an article he published in 1998, "recognized a difference between treating minimal disease and using an agent in maintenance therapy." Decision at 29-30. This finding was clearly erroneous. The Patent Owner cites the following passage from Dr. Grossbard's article:

> [Monoclonal antibodies] may eventually have a greater role in conjunction with conventional cytotoxic chemotherapy or in the minimal disease setting, in which the problems of tumor bulk and circulating disease can be avoided. Maintenance therapy may be another possible use for these agents, although antigen mutation or modulation may limit repetitive administration.

Id. at 29-30; Prelim. Resp. 13-14 (both quoting Ex. 2008 at 3704).

While the Patent Owner relies on nothing more than a syntactic argument to attempt to create a distinction between MRD and maintenance therapy, Dr. Grossbard's statement is entirely facially consistent with the notion that

maintenance therapy was a well-known way of treating MRD, particularly when read in the context of prior art of record. Dr. Grossbard's article does not say or suggest that the use of monoclonal antibodies in a "minimal disease setting" and the use of such antibodies in maintenance therapy are somehow mutually exclusive, as Patent Owner contends. Moreover, although Dr. Grossbard states that antigen mutation or modulation "may" limit repetitive administration of certain monoclonal antibodies, Dr. Grossbard does not describe to what extent it "may" be limited, and certainly does not say or suggest that repetitive administrations should be altogether avoided. Indeed, McLaughlin established that repeated administration of rituximab is effective and further suggested that six months would be an appropriate interval between courses of rituximab maintenance therapy. Ex. 1002 at ¶¶ 95-97; Pet. at 27. The Board misapprehended this evidence at the behest of Patent Owner.

3. Using Rituximab as a Maintenance Therapy Following CVP Chemotherapy Induction Was Obvious in View of McLaughlin and McNeil

McLaughlin teaches the use of rituximab as a maintenance therapy for LG-NHL patients by virtue of disclosing the use of rituximab to treat MRD as a "consideration" for the person of ordinary skill. *See* Section III.A.1 *supra.* In addition, the Board has recognized that McNeil discloses administering a "maintenance regimen—Rituxan every 6 months for 2 years," as claimed. *See*

Decision at 15 (quoting Ex. 1005 at 266). However, the Board concluded that the combination of McLaughlin and McNeil does not teach or suggest using rituximab as a maintenance therapy ***following CVP induction therapy***, even though "CVP was one of [only] two preferred chemotherapy treatments for LG-NHL." *Id.* at 33. This conclusion was based on a misapplication of the law of obviousness.

In his declaration, Dr. Grossbard explained that, as of August 1998, CVP and CHOP were the two standard chemotherapy regimens frequently used to treat LG-NHL patients. Ex. 1002 at ¶ 55. He explained further that by 1996, CVP had become the "most popular" combination therapy among oncologists for treating at least one type of LG-NHL. *Id.* Further, Dr. Grossbard testified that, due to CVP's reduced toxicity profile compared to CHOP, one of ordinary skill would have appreciated the benefits that CVP conferred over CHOP for the treatment of LG-NHL prior to August 11, 1998. *Id.* ("Because of CVP's reduced toxicity profile relative to that of CHOP's, among other things, CVP was known before the Cut-off Date to be more beneficial and appropriate for the treatment of LG-NHL . . . ."); *see* Ex. 1011 at 1 (indicating that chemotherapy of moderate intensity like CVP is preferred for LG-NHL); *see also* Decision at 33 (citing Ex. 1011); Petition at 17, 36, 47, 49 (citing Ex. 1011).

Despite these teachings, the Board found that McLaughlin's disclosure of using "standard" chemotherapies would not teach or suggest to one of ordinary

skill to use CVP before rituximab maintenance therapy. It is well-settled, however, that an invention may be obvious under § 103 if it was "obvious to try" in view of a finite number of identified solutions and a reasonable expectation of success:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007).

Here, the evidence shows only two standard chemotherapies were administered to treat LG-NHL patients: CVP and CHOP. Moreover, CVP was known to have a reduced toxicity profile compared to CHOP and, for this reason, was considered by many to be "more beneficial and appropriate" for treating LG-NHL during the relevant time period. Ex. 1002 at ¶ 55. Accordingly, there can be no genuine dispute that there were a "finite number of identified, predictable solutions," as there were only two preferred chemotherapy options, and a reasonable expectation of success when using rituximab maintenance therapy following a preferred, less toxic induction therapy (*i.e.*, CVP). *KSR*, 550 U.S. at 421. At minimum, it would have been obvious for a person of ordinary skill to try

CVP as the chemotherapy in view of the teachings of McLaughlin and McNeil, since it was one of only two options and known to have lower toxicity than CHOP.

B. The Purported Synergy Between CHOP and Rituximab Relates to Combination Therapies and Not Maintenance Therapies

The Board's denial of institution based on the combination of McLaughlin and McNeil was based in large part on a misapprehension of "evidence in the prior art of synergy between the doxorubicin component of CHOP and rituximab" provided and argued by Patent Owner. *See* Decision at 19, 34.

The Board accepted as true certain evidence submitted by Patent Owner purporting to show that "the doxorubicin component in CHOP therapy was known to act synergistically with rituximab." *See id.* at 19 (citing Ex. 2021; Ex. 2023); *see also id.* at 34. While the two journal articles cited by Patent Owner refer to an *in vitro* synergy between rituximab and doxorubicin (*see* Ex. 2021 at 7; Ex. 2023 at 550), these articles describe ***combination therapies*** in which rituximab and the chemotherapeutic agents (*i.e.*, CHOP) were administered to the patient ***in concert***. *See* Ex. 2021 at 7; Ex. 2023 at 550. Patent Owner also alleged, and the Decision accepted as true, that McLaughlin would have "discouraged the skilled person from omitting doxorubicin" because "McLaughlin teaches that CHOP [together] with rituximab should be used in patients with LG-NHL because the regimen showed good response without increasing toxicity." Prelim. Resp. at 53

(citing Ex. 1009 at 2831). But again, the portion of McLaughlin cited by Patent Owner describes a study that administered rituximab and CHOP as ***a combination therapy***—an entirely different clinical setting. In fact, the study discussed in McLaughlin is titled, "Chemoimmunotherapy of low-grade lymphoma with the anti-CD20 antibody ***IDEC-C2B8 in combination with CHOP chemotherapy***." Ex. 1009 at 2831 (citing Ex. 1054) (emphasis added).

Neither McNeil, nor claim 1 of the '172 patent, involves the contemporaneous administration of rituximab and chemotherapeutic agents. Claim 1 requires ***first*** administering CVP to induce remission of LG-NHL, and ***then*** administering rituximab every six months over two years to maintain remission. The treatments steps are sequential. Because the chemotherapeutic agents (CHOP) and rituximab are not administered together as a combination therapy in the claimed method, the alleged synergy between rituximab and the doxorubicin component of CHOP is not relevant to the obviousness analysis, or whether a skilled artisan would modify McNeil to use CVP instead of CHOP therapy.

Moreover, one of ordinary skill would not be discouraged from using CVP ***before*** rituximab because any "synergy" that may exist from the concurrent administration of CHOP and rituximab would not exist in a therapy involving the administration of chemotherapy agents ***followed by*** rituximab many months later as a maintenance therapy, as recited in claim 1 of the '172 patent.

C. McNeil Teaches Less Toxic Alternatives to CHOP, Including the Omission of Doxorubicin to Reduce Toxicity

The Board also misapprehended the teachings of McNeil regarding less toxic alternatives to CHOP and overlooked McNeil's explicit teachings regarding the removal of the doxorubicin component of CHOP. The Board correctly notes: "McNeil expressly taught reducing toxicity by performing mini-CHOP . . . ." *See* Decision at 34. Importantly, however, the Board incorrectly found that McNeil does not expressly teach "removing the doxorubicin component of that [CHOP] regimen." *Id.* As part of McNeil's discussion regarding "the search for other drug combinations that may be as effective but less toxic than CHOP," the reference describes a trial in which the doxorubicin in CHOP was substituted by a less toxic alternative. Ex. 1005 at 267. Thus, even before McNeil mentions "mini-CHOP" as an alternative strategy to reduce toxicity, McNeil acknowledges the importance of finding other drug combinations "as effective but less toxic than CHOP" and expressly teaches the removal of doxorubicin to reduce toxicity. *Id.*

The motivation for a person of ordinary skill to modify McNeil's process to arrive at the process recited in claim 1 of the '172 patent is explicitly provided in the prior art, where McNeil teaches substituting CHOP components and omitting doxorubicin to lower toxicity. *See id.* CVP was "one of two preferred chemotherapy treatments for LG-NHL," as the Board has acknowledged (*see* Decision at 33), and Petitioners have provided ample evidence that a person of

ordinary skill would have known that omitting the doxorubicin component of CHOP and using CVP to treat LG-NHL would reduce toxicity (*see* Pet. at 3-4, 32, 36-37 (citing Ex. 1002 at ¶¶ 41, 55, 65-69, 121)).

Finally, to the extent the Board limited the skilled artisan to a single less-toxic alternative to CHOP—namely, "mini-CHOP"—this was legally erroneous. *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1376 (Fed. Cir. 2013) ("[A] finding that the prior art as a whole suggests the desirability of a particular combination need not be supported by a finding that the prior art suggests that the combination claimed . . . is the preferred, or most desirable, combination.") (quoting *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004)).

V. CONCLUSION

Petitioners respectfully request that the Board grant this request for rehearing and modify the Decision to institute *inter partes* review based upon the combination of McLaughlin (Ex. 1009) and McNeil (Ex. 1005).

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CERTIFICATE OF SERVICE

I hereby certify that on this 12th day of August 2015, a copy of this PETITONER'S REQUEST FOR REHEARING ON THE INSTITUTION DECISION UNDER 37 C.F.R. §42.71(d) has been served in its entirety on counsel of record for patent owner via email (as agreed by the parties) at the following email addresses:

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