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Paper No. 8
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

BIOGEN, INC.,
Patent Owner.

Case IPR2017-01167
Patent 8,557,244 B1

Before ERICA A. FRANKLIN, SHERIDAN K. SNEDDEN, and JACQUELINE T. HARLOW, *Administrative Patent Judges*.

FRANKLIN, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Pfizer, Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1 and 2 of U.S. Patent No. 8,557,244 B1 (Ex. 1001, "the '244 patent"). Paper 2 ("Pet."). Biogen, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 7 ("Prelim. Resp.").

We have authority under 35 U.S.C. § 314 to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); *see also* 37 C.F.R. § 42.4 (a). Upon considering the Petition and the Preliminary Response, we determine that Petitioner has not shown a reasonable likelihood that it would prevail in showing the unpatentability of claims 1 and 2. Accordingly, we deny the Petition and decline to institute an *inter partes* review.

A. Related Proceedings

Petitioner and Patent Owner have not identified any pending district court proceeding involving the '244 patent. Pet. 4; Paper 5, 2. Another petitioner filed petitions for *inter partes* review of claims of the '244 patent (IPR2017-01094) (institution denied, Paper 12) and related U.S. Patent Nos. 8,329,172 B2 (the '172 patent') (IPR2017-01093) (institution denied, Paper 12) and 9,296,821 B2 (IPR2017-01095) (institution granted, Paper 12). The current Petitioner has filed a petition for *inter partes* review of claims of the '172 patent (IPR2017-01166) and of U.S. Patent No. 8,821,873 B2 (IPR2017-01168).

B. The '244 Patent

The '244 patent relates to a method of treating a patient who is greater than 60 years old and has diffuse large cell lymphoma ("DLCL"), along with bulky disease (tumor > 10 cm in diameter). Ex. 1001, 8:41–47. The treatment comprises administering an unlabeled chimeric anti-CD20

antibody and CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy. *Id*. In particular, a preferred antibody is rituximab. *Id*. at 8:48–49.

C. Challenged Claims

Claims 1 and 2 of the '244 patent are reproduced below:

> 1. A method of treating a patient with diffuse large cell lymphoma, comprising administering an unlabeled chimeric anti-CD20 antibody and CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient, wherein the patient is > 60 years old and has bulky disease (tumor >10 cm in diameter).
>
> 2. The method of claim 1, wherein the chimeric antibody is rituximab.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1 and 2 of the '244 patent on the following grounds:

Claims	**Basis**	**References**
1 and 2	§ 103	Shipp, [1] Link,[2] and McNeil[3]

[1] Shipp et al., *High-Dose CHOP as Initial Therapy for Patients with Poor-Prognosis Aggressive Non-Hodgkin's Lymphoma: A Dose-Finding Pilot Study*, 13 J. CLIN. ONCOL. 2916–23 (1995) (Ex. 1009).
[2] Link et al., *Phase II Pilot Study of the Safety and Efficacy of Rituximab in Combination with CHOP Chemotherapy in Patients with Previously Untreated Intermediate- or High-Grade NHL, Program/Proceedings*, 17 AM. SOC. CLIN. ONCOL. 3a (Abstract 7) (1998) (Ex. 1005).
[3] McNeil, *Non-Hodgkin's Lymphoma Trials In Elderly Look Beyond CHOP*, 90 J. NAT. CANCER INST. 266–67 (1998) (Ex. 1003).

Claims	Basis	References
1 and 2	§ 103	Shipp and Coiffier[4]

Petitioner also relies upon the Declarations of Howard Ozer, M.D., Ph.D. (Ex. 1002) and Scott Bennett, Ph.D. (Ex. 1016).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner asserts that the broadest reasonable interpretation of the claim terms is their plain and ordinary meaning. Pet. 26. Elsewhere in the Petition, Petitioner states that skilled artisan would have recognized that

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[4] Coiffier et al., *Rituximab (Anti-CD20 Monoclonal Antibody) for the Treatment of Patients with Relapsing or Refractory Aggressive Lymphoma: A Multicenter Phase II Study*, 92 BLOOD 1927–32 (1998) (Ex. 1006).

"DLCL would be categorized as an intermediate- or high-grade NHL according to the Kiel classification as well as the REAL classification, or as a 'working formulation' ('WF,' sometimes labeled 'IWF) type 'G' lymphoma." Pet. 9–10. Patent Owner agrees that the plain and ordinary meaning applies to the term "diffuse large cell lymphoma," and further adds that such meaning is that the term refers to a single, unique NHL subtype, e.g., "IWF Grade G," and does not include "'diffuse mixed cell lymphoma' (IG-NHL of IWF Grade F)" or "'immunoblastic lymphoma' (IG-NHL of IWF Grade H)." Prelim. Resp. 22–25. In support of their assertions, Petitioner and Patent Owner rely on Hiddemann's disclosure of the three major classifications of NHL. Pet. 9 and Prelim. Resp. 23 (both citing Ex. 1011, 2, Table 1).[5] One of these major classification systems is "Working formulation." Ex. 1011, 2, Table 1. Hiddemann identifies diffuse large cell NHL, under that "Working formulation" classification system as being represented only by "G." *Id*.

Thus, we agree with Petitioner's and Patent Owner's assertions and, for purposes of this Decision, we construe "diffuse large cell lymphoma" under the "Working formulation" (IWF) to be represented only by an IWF Grade G designation and does not include diffuse mixed cell NHL (IWF Grade F) or immunoblastic, large cell NHL (IWF Grade H).

In view of our analysis, we determine that construction of additional claim terms is not necessary for purpose of this Decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (Only

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[5] Hiddemann, *Non-Hodkin's Lymphoma–Current Status of Therapy and Future Perspectives*, 31A EUROPEAN J. CANCER 2141-45 (1995) (Ex. 1011) (citation above refers to page numbers assigned by Petitioner).

terms which are in controversy need to be construed, and only to the extent necessary to resolve the controversy).

B. Obviousness over Shipp, Link, and McNeil

Petitioner asserts that claims 1 and 2 would have been obvious over Shipp and Link. Pet. 36–44.

1. Shipp

Shipp describes a pilot study having a goal of developing a more effective approach to the treatment of patients with poor-prognosis aggressive NHL. Ex. 1009, 1. More particularly, the study was designed to first determine the maximum-tolerated dosage (MTD) of a CHOP regimen with granulocyte colony-stimulating factor (G-CSF) support, and then to assess preliminarily the efficacy of the regimen. *Id*. Patients enrolled in the study had tumor involvement ≥ 10 cm, and advanced-stage aggressive NHL (either diffuse mixed, diffuse large-cell, or large-cell immunoblastic lymphoma). *Id*. at 2. Four of the 30 patients enrolled in the study were age 60 or over. *Id*. at 3, Table 1 (patient nos. 2, 6, 11, and 14). Three of those elderly patients had tumor involvement of 10 cm, and one had tumor involvement of 13 cm. *Id*.

Patients received one of four high-dose levels of cyclophosphamide and/or doxorubicin. *Id*. Dose level three was determined to be the MTD after the single patient on the highest dose level four experienced severe cumulative thrombocytopenia. *Id*. at 4. Shipp explains that in 22 patients treated at the MTD, 86% achieved an initial complete response (CR) and 79% of those complete responders, and 69% of all patients remained progression-free with 20 months median follow-up. *Id*. at 6. Shipp states, "Our preliminary analysis suggests that patients who are less likely to

benefit from standard therapy may have a higher CR rate with the high-dose CHOP regimen." *Id*. at 7.

2. Link

Link describes a phase II pilot study of the safety and efficacy of administering Rituxan in combination with CHOP chemotherapy to 31 patients with previously untreated intermediate- or high-grade NHL. Ex. 1005, 3a (Abstract 7). Patients had a median age of 49 and included those with a pathology of IWF G (DLCL). *Id*. Link describes Rituxan as "rituximab, IDEC-C2B8," a chimeric monoclonal antibody that targets the CD20 antigen expressed on normal and malignant B-cells. *Id*.

Link reports that the study resulted in 19 patients having a complete response, 10 patients having a partial response, and one patient with progression. *Id*. According to Link, the study regimen "represents a tolerable therapy . . . and may offer higher response rates" than seen with conventional CHOP therapy alone. *Id*.

3. McNeil

McNeil describes a randomized trial for elderly patients with intermediate-grade NHL involving a combination treatment of CHOP and Rituxan (IDEC-C2B8). Ex. 1003, 266. McNeil explains that the trial, organized by the Eastern Cooperative Oncology Group ("ECOG"), "will recruit 630 patients age 60 and over" to receive the combination therapy. *Id*.

4. Analysis

Petitioner asserts that Shipp disclosed the use of CHOP to treat DLCL patients with bulky disease. Pet. 38 (citing Ex. 1002 ¶¶ 76–81). According to Petitioner, Shipp teaches that CHOP "could be more effective in patients with bulky disease at higher doses without the toxicity of other

chemotherapy drugs." *Id*. (citing Ex. 1009, 1). Petitioner asserts further that Shipp taught that its CHOP therapy could be used to treat patients over 60 years of age having intermediate grades of lymphoma, such as DLCL, who also have bulky disease. *Id*. at 38–39 (citing Ex. 1002 ¶¶ 51–52). According to Petitioner, Shipp's study included four patients age 60 years or older "with bulky disease ≥ 10 cm," and at least three of them responded to its high-dose CHOP therapy. *Id*. at 38–39 (citing Ex. 1009, 6, Table 6; Ex. 1002 ¶51).

Petitioner asserts that "Link studied the combination of CHOP and rituximab . . . in 21 patients with DLCL, among other patients," and determined that "the combination of CHOP and rituximab successfully treated patients with DCLC," without exposing the patients to greater levels of toxicity than experienced with CHOP alone. *Id*. at 40. According to Petitioner, a person of skill in the art would have been motivated by Link to add the rituximab to the therapy taught by Shipp to treat patients over 60 with DLCL accompanied by bulky disease to increase treatment efficacy and to decrease its toxicity. *Id*. at 40–41. Petitioner asserts that McNeil confirms the motivation for a POSA to combine Shipp and Link by describing a need in the art to develop treatments for older patients that improve efficacy without increasing toxicity, as older patients were known to experience poorer outcomes with CHOP due to its toxicity. *Id*. at 41.

Additionally, Petitioner asserts that it would have been obvious to combine rituximab with Shipp's CHOP treatment because the two drugs have separate mechanisms of action. *Id*. at 42 (citing *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1351 (Fed. Cir. 2013) (when it is "well-known in the art that two drugs having different mechanisms for

attacking [the disease] may be more effective than one," it is "obvious to try combination therapy.").

Patent Owner asserts that the combination of Shipp, Link, and McNeil fails to teach or suggest any treatment of DLCL in an elderly patient having bulky disease. Prelim. Resp. 30. According to Patent Owner, Petitioner's reliance on Shipp as teaching each element of claim 1, except for the use of an anti-CD20 antibody is unsupported. *Id*. at 11, 30. In particular, Patent Owner asserts that Shipp does not identify the NHL histology, i.e., whether DLCL, for the 4 patients in its study aged 60 and older. *Id*. at 11. Further, Patent Owner asserts only 1 of those 4 elderly patients had bulky disease characterized by a tumor > 10 cm in diameter, as required by the claim. *Id*. at 13.

Patent Owner asserts also that Link's discussion of treating DLCL patients does not cure the deficiencies of Shipp because Link does not disclose any patient over 60 years of age, or any patient with bulky disease. *Id*. at 16. Moreover, Patent Owner asserts that, insofar as Link teaches or suggests effectively combining CHOP with rituximab to treat DLCL without added or untolerable toxicity, that combination involved a standard dose of CHOP and not a high-dose as used with Shipp's treatment method. *Id*. at 17–18. As for McNeil, Patent Owner asserts that its teachings would not have given a person of ordinary skill in the art a reason to treat an elderly NHL patient with Shipp's high-dose CHOP because McNeil explained that elderly patients have a hard time even completing a regimen involving standard doses of CHOP due to toxicity. *Id*. at 20 (citing Ex. 1003, 2).

Having considered the arguments and the evidence, we agree with Patent Owner that Petitioner has not shown a reasonable likelihood of

prevailing in establishing that the challenged claims are obvious over the combination of Shipp, Link, and McNeil. In particular, we agree with Patent Owner that Petitioner has not supported its assertion that Shipp teaches all of the elements of claim 1, except for including rituximab in the treatment method. According to Petitioner, "Shipp disclosed that CHOP therapy was the standard of care for DLCL patients with bulky disease, even for patients over 60 years old with intermediate-grade lymphomas such as DLCL accompanied by bulky disease." Pet. 39. However, Shipp does not disclose whether any of those elderly patients has DLCL. Rather, Shipp explains only that patients in the study have one of a variety of forms of aggressive NHL, i.e., "diffuse mixed, diffuse large-cell, or large-cell immunoblastic lymphoma." Ex. 1009, 2; *see also* Table 1 "Characteristics of the Protocol Patients").

Indeed, Petitioner's declarant, Dr. Ozer, acknowledges that "Shipp does not say whether these elderly patients had 'diffuse,' 'diffuse large cell,' or 'immunoblastic large cell' lymphoma." According to Dr. Ozer, Shipp's failure to distinguish which patients had which disease "reflects the understanding of those in the art that there were no significant distinctions in treating these three intermediate and high-grade lymphomas (types F, G, H), all of which are very similar." Ex. 1002 ¶ 52. However, Dr. Ozer has not identified any discussion in Shipp to support that reasoning, or referred us to any other evidence to support that assertion. Without more, we do not accord persuasive weight to Dr. Ozer's opinion that the understanding of those in the art is that there are "no significant distinctions in treating" the three intermediate and high-grade lymphomas disclosed in Shipp.

Link does not cure the deficiency in Shipp as the reference does not teach treating patients over 60 years of age with DLCL accompanied with bulky disease. Although McNeil discussed NHL patients over 60 years of age, McNeil does not disclose those patients as having DLCL or bulky disease. Moreover, Petitioner's combination of the cited references does not rely on Link or McNeil as supplying a teaching or suggestion to treat elderly patients having DLCL and bulky disease with CHOP.

Petitioner also refers to portions of the '244 patent specification as alleged "concessions that chemotherapy was already used in the prior art to treat patients with DLCL accompanied with bulky disease." Pet. 36–38. Even if we considered the referenced portions of the background section of the Specification, those disclosures would not supply the teaching missing in Petitioner's combination of Shipp, Link, and McNeil, i.e., treating a patient over 60 years of age with DLCL and bulky disease by administering CHOP, much less in combination with rituximab. Indeed, as the Patent Owner asserts, the background section of the specification does not mention CHOP, rituximab, DLCL or patients over 60 years of age. Prelim. Resp. 29.

Further, to the extent that Petitioner asserts that it would have been obvious to combine rituximab with CHOP because of their separate mechanisms of action, we remain unpersuaded. Pet. 43. In support of that assertion, Petitioner refers to *Novo Nordisk* , 719 F.3d at 1351. However, in *Novo Nordisk*, the principle upon which Petitioner relies involves a situation wherein two drugs have different mechanisms of treating the *same disease*. *Id*. (obvious to try combination therapy when it was "well-known in the art that two drugs having different mechanisms for attacking diabetes may be more effective than one"). Petitioner has not shown that it was well-known

in the art that either CHOP or rituximab treat, i.e., attack, DLCL presenting with bulky disease in patients over 60 years of age.

Thus, based on the information presented, we determine that Petitioner has not shown sufficiently that there is a reasonable likelihood that it would prevail in showing the unpatentability of claims 1 and 2 over Shipp, Link, and McNeil.

C. Obviousness over Shipp and Coiffier

Petitioner asserts that claims 1 and 2 would have been obvious over Shipp and Coiffier. Pet. 44–50.

1. Coiffier

Coiffier is a journal article discussing a phase II study to evaluate the efficacy and tolerability of rituximab in patients with more aggressive types of lymphoma. Ex. 1006, 1. Of the 52 patients in the study, 30 had DLCL. *Id*. at 2 and 3, Table 3. Of the 52 patients in the study, 5 patients had tumors greater than 10 cm in diameter. *Id*. at 3, Table 3. Patients received eight weekly infusions of either a standard or higher dose of rituximab. *Id*. at 1, 6. Coiffier explains that there were no responses observed in patients whose largest tumor was greater than 10 cm in diameter. *Id*. at 4. As for the results in the remaining patients, Coiffier concludes that the results of the study "indicate that rituximab therapy has significant anti-lymphoma activity in DLCL and [mantle cell lymphoma] patients without the toxicity commonly observed with combination chemotherapy regimens." *Id*. at 6.

2. Analysis

Here again, Petitioner asserts that "Shipp taught all of the elements of claim 1 with the exception of using a monoclonal antibody like rituximab in combination with CHOP therapy." Pet. 44. For the same reasons set forth in section II. B., above, we disagree with Petitioner as Shipp does not disclose whether the patients over 60 years of age included in that study also had DLCL, and Petitioner and Dr. Ozer have not shown sufficiently that a person of skill in the art would have understood that to be the case. Petitioner does not rely on Coiffier to address that deficiency. Rather, Petitioner relies on Coiffier as providing a motivation to combine rituximab to the regimen disclosed by Shipp. Pet. 45–46.

Thus, based on the information presented, we determine that Petitioner has not shown sufficiently that there is a reasonable likelihood that it would prevail in showing the unpatentability of claims 1 and 2 over Shipp and Coiffier.

III. CONCLUSION

For the foregoing reasons, we conclude that the information presented in the Petition does not establish a reasonable likelihood that Petitioner would prevail in showing that claims 1 and 2 of the '244 patent are unpatentable.

ORDER

Accordingly, it is hereby:

ORDERED that Petitioner's request for an *inter partes* review of claims 1 and 2 of the '244 patent is *denied*.

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