UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

BIOGEN, INC.,
Patent Owner.

Inter Partes Review No. IPR2017-01168
Patent No. 8,821,873

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

TABLE OF CONTENTS

TABLE OF AUTHORITIES iii

I. INTRODUCTION 1

II. ARGUMENT 4

A. Patent Owner's response confirms that all claims would have been obvious to a POSA in view of the grounds art. 4

1. This petition will not turn on the POSA definition. 4

2. Moreau teaches each element required by claim 1 except for the use of rituximab. 6

3. The prior art would have motivated a POSA to add rituximab to CHOP in the Moreau regimen. 9

4. A POSA would have reasonably expected success when adding rituximab to CHOP in the Moreau regimen. 12

5. Claims 2, 3 and 5 are obvious for the same reasons claim 1 is obvious. 16

6. Claim 4, which requires bone marrow involvement, likewise would have been obvious. 16

7. At a minimum, all claims were obvious to try. 17

B. Patent Owner's remaining arguments are legally and factually flawed. 20

III. CONCLUSION 24

TABLE OF AUTHORITIES

Page(s)

Cases

Alcon Research Ltd. v. Apotex Inc.,
687 F.3d 1362 (Fed. Cir. 2012) 15

Allergan, Inc. v. Sandoz Inc.,
726 F.3d 1286 (Fed. Cir. 2013) 14, 19

In re Anthony,
414 F.2d 1383 (C.C.P.A. 1969) 14, 19

Bayer Pharma AG v. Watson Labs., Inc.,
874 F.3d 1316 (Fed. Cir. 2017) 14

Bayer Schering Pharma AG v. Barr Labs., Inc.,
575 F.3d 1341 (Fed. Cir. 2009) 19

Daiichi Sankyo, Ltd. v. Apotex, Inc.,
501 F.3d 1254 (Fed. Cir. 2007) 4, 5

In re Gurley,
27 F.3d 551 (Fed. Cir. 1994) 23, 24

Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.,
821 F.3d 1359 (Fed. Cir. 2016) 3, 13

KSR Int'l Co. v. Teleflex Inc.,
550 U.S. 398 (2007).....4, 15, 17, 19

Merck & Co. v. Teva Pharm. USA, Inc.,
395 F.3d 1364 (Fed. Cir. 2005) 14

Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.,
719 F.3d 1346 (Fed. Cir. 2013) 11

Nuvasive, Inc. v. Warsaw Orthopedia, Inc.,
IPR2013-00395, Paper 36 (PTAB Dec. 17, 2014) 3, 13

In re O'Farrell,
853 F.2d 894 (Fed. Cir. 1988) 16

Statutes

35 U.S.C. § 103.....4

I. INTRODUCTION

This dispute turns on whether "a person of skill in the art would have found it obvious to modify Moreau's treatment method to further improve the efficacy of that method"—specifically, by "combining rituximab with Moreau's reduced CHOP regimen to improve the regimen['s] efficacy without adding toxicity." Dec. Inst. 10. The Board "conclude[d] that the information presented in the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that claims 1-5 of the '873 patent are unpatentable" as obvious. *Id.* at 12. Discovery has confirmed that the challenged claims would have been obvious.

To recap, claims 1-5 generally cover methods of treating DLCL patients older than 60 with CHOP along with rituximab in combination with a stem cell transplantation regimen. Moreau teaches a regimen of successfully treating some DLCL patients older than 60 with CHOP in combination with a stem cell transplantation regimen. Thus, the patent claims would have been obvious if the prior art motivated a POSA to improve the Moreau regimen by adding rituximab to CHOP, with a reasonable expectation of success.

The claimed invention was obvious because, among other reasons, rituximab (1) was known to be safe and effective in DLCL patients over 60 (Coiffier), (2) was known to be safe and effective when combined with CHOP in DLCL patients (Link), (3) was actually being used in combination with CHOP in DLCL patients over 60 in

a large-scale Phase III study (McNeil), and (4) was also suggested to be useful in transplantation regimens (Maloney).

Patent Owner and its expert, Dr. Brad Kahl, have not refuted Petitioner's showing of obviousness. As confirmed by Dr. Kahl, there is no dispute that the Moreau regimen teaches all claim limitations except for the use of rituximab. Ex. 1034, 71:19–73:10. As for adding rituximab, Dr. Kahl admitted a POSA would have known from the prior art that rituximab and CHOP were "combinable" in the claimed population due to non-overlapping toxicities and different mechanisms of action, and together resulted in effectively treating a "high number" of DLCL patients. *Id.* at 89:13-17, 92:16, 98:15-24, 114:21-24. A POSA would have been motivated to add rituximab to the Moreau regimen because the prior art taught that adding rituximab to CHOP would not add to the toxicity or affect marrow reserves, and could possibly lead to better results. Ex. 1035 ¶¶ 27-28. Thus, adding rituximab to the Moreau regimen would have been obvious.

Instead of disputing the key prior-art teachings, Patent Owner urges the Board to adopt a heightened—and erroneous—legal standard. According to Patent Owner, Petitioner must prove that a POSA would have reasonably expected the claimed method to be "better than" prior-art methods, such as the Moreau regimen. Resp. 3. Dr. Kahl echoed this approach at deposition, testifying that his "definition of success would mean that the outcome was improved over what would have been achieved

with a standard approach." Ex. 1034, 58:21-23. But that is not what the law requires. A POSA only needed to have a reasonable expectation that adding rituximab to the CHOP in Moreau would successfully "treat[] a patient," as claimed in the '873 patent—not that this combination would improve results from prior art. This is because "[t]he reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). That is, "the obviousness inquiry does not require an advantage or an improvement in properties." *Nuvasive, Inc. v. Warsaw Orthopedia, Inc.*, IPR2013-00395, Paper 36, at 32 (PTAB Dec. 17, 2014).

When properly applied, the legal standard is easily satisfied here, because the Moreau regimen successfully treated four out of the seven patients over 60 with DLCL who received CHOP and transplantation. A POSA would have reasonably expected at least equal, if not better, success by adding rituximab to CHOP in the Moreau regimen. Ex. 1035 ¶ 27.

Patent Owner also argues, in essence, that the prior art taught away from the claimed invention due to toxicity concerns, different dosing schedules, and a purported inability to assess a patient's chemosensitivity. But the prior art and a publication by Patent Owner's own expert refute these assertions. Regardless, Patent Owner never even attempts to, and cannot, meet the strict legal standard for

teaching away. Nor does Patent Owner make any argument that the results of this combination—all of whose elements were known in the art—was somehow unexpected, or that there are other secondary considerations. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007) (where "a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious.").

In sum, the Board should issue a final written decision finding claims 1-5 of the '873 patent unpatentable under 35 U.S.C. § 103 as obvious over the grounds art, i.e., Moreau, Link, McNeil, Maloney, and Coiffier.

II. ARGUMENT

As shown below, it would have been obvious to add rituximab to CHOP in the Moreau regimen, thus rendering all claims of the '873 patent unpatentable.

A. Patent Owner's response confirms that all claims would have been obvious to a POSA in view of the grounds art.

1. This petition will not turn on the POSA definition.

Patent Owner criticizes Dr. Ozer's definition of a POSA, but this criticism is misplaced and, regardless, legally irrelevant. Patent Owner disputes that a POSA includes an oncologist with experience "researching" NHL treatments, arguing that this is "a person whose skill in the art was extraordinary." Resp. 15 (citing Ex. 1002 ¶ 15). Yet in *Daiichi Sankyo, Ltd. v. Apotex, Inc.*, the Federal Circuit reversed, as

clear error, a district court's finding that a POSA only would have been treating patients and not researching treatments where "most of the written description details the inventors' testing" in clinical trials and such "testing is traditionally outside the realm of a general practitioner." 501 F.3d 1254, 1257 (Fed. Cir. 2007). Here, too, the written description details clinical trial testing. Ex. 1001, 7:11-8:35. As in *Daiichi*, a POSA for purposes of the '873 patent also would have had clinical research expertise.

In any event, Dr. Ozer indisputably is qualified to offer opinions from the perspective of a POSA under either side's POSA definition, and Dr. Kahl does not contend otherwise. Ex. 2011 ¶¶ 21-25. In contrast, Patent Owner's expert does not satisfy either definition of a POSA—which requires a "practicing oncologist." Ex. 1034, 27:3-5 (testifying that he is a hematologist, not an oncologist).[1]

[1] Patent Owner tries to discredit Dr. Ozer by citing clearly mistaken testimony that he did not read the patent before filing his declaration. Dr. Ozer obviously misconstrued the question. Not only did Dr. Ozer repeatedly quote and discuss the patent in his declaration, he also cited it in his materials considered. Ex. 1002, 4. To be sure, as Dr. Ozer explained in response to Patent Owner's questioning, he "considered the patent afterwards, but not before I gave my opinion." Ex. 2008, 14:17-18. He was referring to the fact that Petitioner asked Dr. Ozer to form his

2. Moreau teaches each element required by claim 1 except for the use of rituximab.

Dr. Kahl confirmed at deposition what the Board preliminarily found—namely, "that Moreau taught all of the elements of claim[] 1, except for the addition of rituximab." Dec. Inst. 9, 11. Dr. Kahl was asked at deposition: "If you read out the term anti-CD20 antibody in claim one and just read the claim and skip over where it says anti-CD20 antibody, are there any differences between that modified claim one and the Moreau reference?" Ex. 1034, 71:19-23. He responded that the only differences were that the patients in Moreau were "limited to age 61 to 65" (conceding that all were older than 60, as the claims require), Moreau "administered a specified number of CHOP chemotherapy cycles" (but the claims do not require a specific number of CHOP cycles), and "Moreau had criteria for moving on to the stem cell transplantation procedure" (also not required by the claims). Ex. 1034, 72:3–73:7. None of these differences is relevant to the obviousness inquiry.

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obviousness opinions from the perspective of a POSA before giving him the patent, thus avoiding any hindsight bias. *See id.* at 70:4-8 ("Just to be clear, prior to signing this report, had you reviewed the '873 patent in forming your opinions in this report? THE WITNESS: Yes.") (objection omitted). If anything, this point bolsters Dr. Ozer's opinions offered from the perspective of a POSA.

Not only did Moreau disclose CHOP and transplantation in DLCL patients over 60, it also disclosed CHOP "in combination with" transplantation. Thus, combining rituximab with CHOP in the Moreau regimen necessarily would result in rituximab being "administered to the patient in combination with stem cell transplantation regimen." Ex. 1001, 8:37-44, 51-56.

As explained in the Petition, the limitation "in combination with" includes administration of rituximab at "induction," which the patent explains comprises "the initial therapies aimed at achieving induction of remission" and "[t]ypically . . . involves the administration of some type of chemotherapy, i.e., CHOP" to achieve remission. Pet. 26, 30-31; Ex. 1001, 6:13-27. Patent Owner agrees that the "in combination with" claim limitation is satisfied when rituximab is administered "at any point in the transplant," including induction. Resp. 17-19; *see also id.* at 19 ("Even administration of an anti-CD20 antibody at an induction stage of a stem cell transplantation regimen can fall within the scope of the claims."); Ex. 2011 ¶ 57 (same). And Dr. Kahl readily conceded that the administration of CHOP in the Moreau regimen "could be considered an induction phase." Ex. 1034, 118:14-15. Adding rituximab to such CHOP administration would make the treatment regimen fall squarely within the scope of the claims.

Patent Owner attempts to avoid obviousness by asserting that claim construction is disputed. But there is no such dispute, much less a dispute that is

material to patentability. According to Patent Owner, Petitioner's claim construction "includes the administration of the anti-CD20 antibody (e.g., rituximab) before the stem cell transplantation," but "the claims require that an anti-CD20 antibody be administered during (*e.g.*, 'at the various stages of') the stem cell transplantation regimen." Resp. 19. That misstates Petitioner's argument.

To be sure, as Patent Owner asserts, Dr. Ozer testified that "claim 1 includes the administration of the anti-CD20 antibody (e.g., rituximab) before the ***stem cell transplantation***, as well as 'rituximab treatment at the various stages of transplantation'…." Resp. 19 (emphasis added). But this testimony is consistent with the parties' construction of "in combination with." Despite Patent Owner's contrary assertions, Petitioner does not argue that claim 1 includes administration of rituximab before all phases of the entire stem cell transplantation ***regimen***. Instead, as Dr. Ozer explained in his initial declaration, the induction phase—which indisputably is part of the stem cell transplantation regimen—precedes the actual stem cell transplantation, which is conducted in the harvest phase of the regimen. Ex. 1002 ¶¶ 25-26; *see also* Ex. 1035 ¶ 25.

As discussed, Dr. Kahl conceded that, in Moreau, CHOP was administered to patients in the induction phase. Ex. 1034, 118:14-15. Thus, combining rituximab

with some or all of the four CHOP doses in the Moreau regimen[2] necessarily would require use of rituximab in the induction phase as well. Again, as Patent Owner concedes, using rituximab in the induction phase of a stem cell transplantation regimen involves using rituximab "in combination with" stem cell transplantation. Resp. 17-19; Ex. 2011 ¶ 56. And it necessarily follows that adding rituximab to CHOP in the Moreau regimen would result in administering rituximab "in combination with [a] stem cell transplantation regimen," as required in claim 1. Patent Owner cannot credibly argue otherwise. Ex. 1001, 8:43-44.

3. The prior art would have motivated a POSA to add rituximab to CHOP in the Moreau regimen.

Dr. Kahl's testimony bolsters Petitioner's argument that it would have been obvious to add rituximab to CHOP in the Moreau regimen in light of the teachings of Link, Coiffier, McNeil and Maloney. First, as previously explained, Link taught

[2] Patent Owner mistakenly argues that Petitioner waived any argument as to the fourth CHOP dose—by purportedly focusing on the first three CHOP doses in the petition. Resp. 25 n.7. Petitioner never limited its obviousness theory to the first three CHOP doses. *See, e.g.*, Pet. 45 ("Link would have motivated a POSA to replace CHOP in Moreau with CHOP plus rituximab."). And the institution decision expressly noted the fourth CHOP dose in Moreau. Dec. Inst. 6.

that rituximab and CHOP were safe and effective in DLCL patients, although the study did not specifically study patients over 60. Ex. 1005, 5. Dr. Kahl confirms that a POSA would have learned from Link that, because rituximab did not add to the toxicity of CHOP, rituximab and CHOP were "combinable." Ex. 1034, 92:9-16.

Second, Coiffier taught that rituximab was both safe and effective in DLCL patients over 60. The authors found that "this first trial of rituximab in DLCL . . . patients experienced a significant clinical activity with a low toxicity," leading to the logical conclusion that rituximab "should be tested in combination with chemotherapy in such patients." Ex. 1006, 1; *see also* Ex. 1035 ¶¶ 26–27. As Dr. Kahl conceded, CHOP was standard chemotherapy for DLCL patients over 60. Ex. 1034, 31:4-23. He further agreed that a POSA could "look at [Coiffier] and look at the toxicity profile and determine that [rituximab] is a tolerable treatment for older patients [ ]—that's just fairly clear from the paper." *Id.* at 114:21-24.

Third, McNeil also suggested combining rituximab with CHOP by disclosing an ongoing Phase III trial combining these drugs in DLCL patients over 60. Ex. 1003, 1. This clinical study made sense because, as Dr. Kahl testified, "[i]n general when you're combining agents in any clinical trial [for] any anticancer regimen you're picking agents that have differing mechanisms of action and nonoverlapping toxicities." Ex. 1034, 89:13-17. As Dr. Kahl further explained, "presumably that

was given consideration when designing clinical trials testing rituximab with CHOP chemotherapy, a mechanism of action consideration." *Id.* 90:14-17.

Indeed, in *Novo Nordisk A/S v. Caraco Pharmaceutical Laboratories, Ltd.*, the Federal Circuit held that where it was "well-known in the art that two drugs having different mechanisms for attacking diabetes may be more effective than one, and so drugs were often tested in combination therapy after demonstrating effectiveness in monotherapy," it would have been obvious to combine the two drugs. 719 F.3d 1346, 1351 (Fed. Cir. 2013). As Dr. Ozer explained in his declaration, that describes the field of oncology, and rituximab and CHOP in particular. Chemotherapeutic drugs and other therapies were routinely tested together, particularly when the drugs had complementary mechanisms of action. Ex. 1002 ¶¶ 37-39, 51, 53-54.

Fourth, Moreau and Maloney suggested combining rituximab and CHOP with stem cell transplantation. Moreau disclosed a successful stem cell transplantation study, and Maloney encouraged adding rituximab to that regimen: "Since this antibody [rituximab] does not appear to impair marrow reserves, it could possibly be used . . . following high-dose chemotherapy with ABMT [autologous bone marrow transplantation] or peripheral stem-cell rescue." Ex. 1008, 10. As Dr. Ozer explained, Maloney "taught that rituximab does not negatively impact stem cell

reserves," suggesting that rituximab was an obvious agent to combine with a stem cell transplantation regimen, such as the one used in Moreau. Ex. 1002 ¶ 92.

Nothing in Maloney suggested that rituximab's impact on stem cell reserves was confined to a particular grade of NHL. Nor did Maloney confine its teaching to administering rituximab ***following*** transplantation, as Patent Owner has contended. Resp. 42; *see also* Ex. 1035 ¶ 28. Thus, Maloney supplies yet another motivation to use rituximab and CHOP in combination with a stem cell transplantation regimen.

4. A POSA would have reasonably expected success when adding rituximab to CHOP in the Moreau regimen.

There is no dispute that the Moreau regimen successfully treated over half of the DLCL patients over 60 in the study who received both CHOP and transplantation; indeed, four of the seven patients over 60 with DLCL had a ***complete*** response to this treatment regimen. Ex. 1007, 3 at Table 3. Although there was room for improvement, the regimen was clearly promising. In the words of Moreau, combining CHOP with a stem cell transplantation regimen was a "feasib[le]" alternative for successfully treating "a patient" over 60 with DLCL. *Id.* at 1; Ex. 1001, 8:37-44.

A POSA would have reasonably expected at least the same, if not greater, success by adding rituximab to CHOP in the Moreau regimen. As explained, Link taught that rituximab combined with CHOP was at least as effective in DLCL

patients as CHOP alone, without added toxicity. Ex. 1005, 5. Coiffer further showed that rituximab was both safe and effective in DLCL patients over 60 and encouraged combining it with chemotherapy (e.g., CHOP). Ex. 1006, 1. And McNeil disclosed a Phase III study of rituximab and CHOP in DLCL patients over 60. Ex. 1003, 1.

Petitioner need not show more to demonstrate a reasonable expectation of success, because this "requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Sys.*, 821 F.3d at 1367. Patent Owner misapplies this standard when arguing that a POSA would not have expected results "better than" prior art therapies. Resp. 27; *see also id.* at 3, 33, 38. Dr. Kahl repeats this error when testifying that his "definition of success would mean that the outcome was improved over what would have been achieved with a standard approach." Ex. 1034, 58:21-23. This is not what the law requires.

Obviousness does not require any expected improvement over the prior art. Instead, the POSA merely needed to have a reasonable expectation of "meet[ing] the limitations of the claimed invention." *Intelligent Bio-Sys.*, 821 F.3d at 1367 (emphasis added); *see also Nuvasive, Inc.*, IPR2013-00395, Paper 36, at 32 ("[T]he obviousness inquiry does not require an advantage or an improvement in properties."). That is clearly the case here. Given that Moreau successfully treated

DLCL patients over 60, a POSA would have reasonably expected the same, if not better, results when using rituximab with CHOP in that same regimen.

To the extent Patent Owner is arguing that the safety and effectiveness of rituximab and CHOP in combination with a stem cell transplantation regimen was not definitively established with clinical data before the prior date, Resp. 3, 27, 33, 38, that too misapplies the relevant standard. "There is no requirement in patent law that the person of ordinary skill be motivated to develop the claimed invention based on a rationale that forms the basis for FDA approval." *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013); *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1326 (Fed. Cir. 2017) ("a lack of FDA approval cannot negate an otherwise apparent motivation to formulate a product"). "Congress has given the responsibility to the FDA, not to the Patent Office, to determine . . . whether drugs are sufficiently safe." *In re Anthony*, 414 F.2d 1383, 1395 (C.C.P.A. 1969). And because the '873 patent "sets forth no human clinical or laboratory data showing the safety and tolerability of the treatment methods claimed," it "adds nothing beyond the teachings of [the prior art]." *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1374 (Fed. Cir. 2005).

Indeed, there is nothing inventive in what Patent Owner claimed. As made clear in Moreau, and confirmed by Dr. Kahl, the listed inventors did not "claim[] to have invented CHOP in combination with stem cell transplantation." Ex. 1034,

65:13-22. Nor did they claim to have invented the concept of improving CHOP's efficacy in DLCL patients over 60 by adding rituximab—a concept encouraged in Link, Coiffier and McNeil. Patent Owner merely claimed the logical next step in the prior art by claiming the obvious combination of these two concepts, without providing the public any evidence that they even tested the claimed combination beforehand. *Id.* at 76:22–77:9; *see also Alcon Research Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012) ("argu[ment] that [the prior art] would not give a skilled artisan an expectation of success because it does not teach that [the claimed drug] is safe for the human eye . . . [was] without merit"; "[w]hile it [was] true that [the art did] not expressly disclose that [the drug] would be safe for use in human eyes, neither d[id] the patent," which was "not based on testing in humans").

In short, when, as here, "a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR*, 550 U.S. at 417. That is particularly true where Patent Owner points to no evidence that this combination of known elements had any unexpected results. Thus, for the reasons discussed above, in the petition, and in Petitioner's expert declarations, a POSA would have had a "reasonable expectation of success" in pursuing the therapy suggested by the prior art that ultimately became the claimed

invention. *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). The Board should find that claim 1 would have been obvious.

5. Claims 2, 3 and 5 are obvious for the same reasons claim 1 is obvious.

Claims 2 and 3 further specify that the anti-CD20 antibody is "chimeric" and is "rituximab." Claim 5, like claim 3, recites CHOP and rituximab in combination with stem cell transplantation in DLCL patients over 60. *See* Resp. 17. Patent Owner does not dispute that the obviousness analysis for claim 1, which relies on prior art discussing rituximab, is substantively identical to the obviousness analysis for claims 2, 3, and 5. Thus, for the reasons discussed above, the Board should find that claims 2, 3, and 5 would have been obvious.

6. Claim 4, which requires bone marrow involvement, likewise would have been obvious.

Claim 4—which requires bone marrow involvement, i.e. the presence of tumors in the bone marrow—similarly was obvious in view of the grounds art, particularly Coiffier's teachings. Pet. 52-53 (citing Ex. 1002 ¶¶ 100-101). Critically, Patent Owner's expert conceded that a POSA would not have expected the treatment to vary regardless of whether the DLCL patient over 60 had bone marrow involvement. In response to the question "[w]ould your treatment of that patient all else being equal be the same as your treatment of a DLCL patient over

age 60 without bone marrow involvement?" Dr. Kahl testified: "Those treatments are likely to be the similar." Ex. 1034, 85:15-16.

This is precisely what a POSA would have expected as of the priority date. Ex. 1035, ¶ 29. Indeed, the testimony of Drs. Kahl and Ozer on this point is confirmed by Coiffier, where all DLCL patients received identical rituximab treatments, even though 43% of those patients had bone marrow involvement. Ex. 1006, 3 at Table 3.

Because it would have been obvious to add rituximab to CHOP in the Moreau reference (thus rendering claims 1-3 and 5 obvious), it would have been equally obvious to practice the method of claim 4. This is because the regimen would be identical with bone barrow involvement. *KSR*, 550 U.S. at 417 (where "a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious.").

7. At a minimum, all claims were obvious to try.

Although the Board need not reach this alternative argument, all patent claims also were obvious to try. Patent Owner disputes that there was a "finite number of identified, predictable solutions" known in the art for treating DLCL patients over 60. *KSR*, 550 U.S. at 421. In particular, Patent Owner asserts that Petitioner "never analyzes the prior art to identify the available options," which includes

chemotherapies other than CHOP. Resp. 53-54. But as Dr. Kahl conceded, CHOP—not the various other chemotherapies listed by Patent Owner—was the standard of care as of the priority date. In 1999, "there are options that are equally effective to CHOP, but they are more toxic than CHOP and so they would not have been a desired alternative." Ex. 1034, 35:3-6. As Dr. Kahl further testified, over half of DLCL patients over 60 would have been candidates for CHOP. *Id.* at 31:4-23. Rituximab was one of only a finite number of options for improving outcomes in such patients who were administered CHOP.

Patent Owner responds by arguing that rituximab was not yet "known" to treat DLCL in patients over 60. Resp. 55. In so arguing, Patent Owner misreads Coiffer as not identifying "any results from using rituximab to treat elderly DLCL patients." *Id.* Dr. Kahl conceded Patent Owner's misreading: A POSA could "look at [Coiffier] and look at the toxicity profile and determine that this is a tolerable treatment for older [DLCL] patients [ ]—that's just fairly clear from the paper." Ex. 1034, 114:21-24; *id*. at 30:2-7 (defining elderly patients as over 60). Indeed, Coiffier expressly taught that rituximab had "significant activity" in such DLCL patients and "should be tested in combination with chemotherapy in such patients." Ex. 1006, 1.

Patent Owner also asserts that transplantation would not "have been a known solution for treating DLCL in elderly patients as of the priority date." Resp. 55. Yet Moreau successfully treated such patients with transplantation. Even if

transplantation "usually" was not used in this population, *id.*, the very point of Moreau was to teach that transplantation was, in fact, a "feasib[le]" alternative for successfully treating "a patient" over 60 with DLCL. Ex. 1007, 1. This treatment solution was thus known, and Patent Owner's effort to argue otherwise misstates the legal standard. *See Allergan*, 726 F.3d at 1292 ("There is no requirement in patent law that the person of ordinary skill be motivated to develop the claimed invention based on a rationale that forms the basis for FDA approval."); *In re Anthony*, 414 F.2d at 1395 ("Congress has given the responsibility to the FDA, not to the Patent Office, to determine . . . whether drugs are sufficiently safe.").

In short, CHOP was the leading chemotherapy for DLCL patients including those over 60, rituximab was known to be effective in such patients and also known to be effective in combination with CHOP, and transplantation was a known method that could be used even with patients over 60. These options were finite and predictable, *KSR*, 550 U.S. at 421, and created a set of therapies that was "small or easily traversed." *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009) (internal quotation marks omitted). At a minimum, therefore, the claims were obvious to try. *KSR*, 550 U.S. at 421.

B. Patent Owner's remaining arguments are legally and factually flawed.

Patent Owner further argues that toxicity concerns, dosing differences, and chemosensitivity issues would have prevented a POSA from adding rituximab to CHOP in the Moreau regimen. Without ever mentioning the words "teaching away," Patent Owner effectively makes a teaching-away argument—without coming close to meeting the legal standard. These arguments are legally and factually meritless.

First, Patent Owner argues a POSA would not have combined rituximab with CHOP in the Moreau regimen because doing so would have "add[ed] significant toxicity." Resp. 36. Dr. Kahl confirmed at deposition, however, that the adverse events observed in Moreau's study were "common," and that the prior art taught that rituximab did not have overlapping toxicity with CHOP. Ex. 1034, 89:13-17, 125:9-14, 126:8-10. As Dr. Kahl further explained, when a drug does not have overlapping toxicities with another therapy, "it . . . means they're combinable." *Id.* at 92:9-16. Thus, a POSA would have been sufficiently motivated to add rituximab to CHOP in the Moreau regimen, and would have reasonably expected that it would be a safe therapy for the claimed patient population.

Second, Patent Owner argues that a POSA would not have been motivated to combine the teachings of Link, McNeil, and Maloney with the teaching of Moreau because the dosing protocols across the references are not identical. *See, e.g.*, Resp.

45 (noting that Coiffier administered 8 weeks doses of rituximab whereas CHOP is administered every 21 days). But Patent Owner's argument is belied by Dr. Kahl's admission that Link and Coiffier supported the rationale for designing the phase III trial disclosed in McNeil—namely, that rituximab and CHOP had non-overlapping toxicity and potentially complementary mechanisms of action. Ex. 1034, 89:7-90:17; 92:1-16; 112:8-18. Thus, as Dr. Kahl confirmed at deposition, not only would a POSA have combined rituximab and CHOP, but doctors in the field were already combining these drugs in a large-scale clinical trial to treat the claimed patient population. *See id.* at 89:13-17, 90:14-17.

Patent Owner also argues that adding rituximab to CHOP in the Moreau regimen would have prevented a POSA from determining whether a patient was chemosensitive—purportedly a necessary step preceding stem cell transplantation. According to Patent Owner, a POSA would proceed with transplantation only if a patient were sensitive to chemotherapy. It follows, according to Patent Owner's argument, that adding rituximab would have "confounded [the chemosensitivity] assessment." Resp. 30. Patent Owner cites no prior art to support this argument, because it is factually unfounded.

As explained by Petitioner's expert, Dr. Soiffer, a POSA in 1999 would have been concerned with ***treatment sensitivity***, not chemosensitivity as such. Ex. 1035 ¶¶ 32–35. To be sure, treatment sensitivity was sometimes referred to as

chemosensitivity at the time because chemotherapy was the only available NHL therapy until the discovery of rituximab. *Id.* ¶ 32. But so long as a patient was responsive to any therapy—for example, rituximab combined with CHOP—the patient was eligible for transplantation following high-dose therapy with that given treatment. *Id.* ¶ 35. Applied here, as Dr. Soiffer explains, if patients given rituximab with CHOP as part of a modified Moreau therapy responded to such an induction regimen, a POSA would have proceeded to transplantation following a high-dose treatment. *Id.* ¶¶ 35–36.

Indeed, as one of Dr. Kahl's own articles confirms, stem cell transplantation can be administered to NHL patients even if they were not sensitive to chemotherapy. According to this article, 23% of NHL patients in the underlying study had "chemotherapy resistant disease," but the protocol nonetheless "allowed [these patients who were not chemosensitive] to move on to stem cell transplantation." Ex. 1033, Kahl at 1, 5; Ex. 1034, 136:9-11; *see also id.* at 134:18-20 (equating chemotherapy resistance and insensitivity). This 1987-2001 study (beginning before the priority date) even included patients over 60. Ex. 1033, Kahl at 2. The study concluded: "Despite including primary induction failures and 15 (23%) patients with ***resistant disease***, patients treated with this regimen had [overall survival] and [event-free survival] that appear similar to previously published studies of [high-dose chemotherapy] in NHL." Ex. 1033, Kahl at 5 (emphasis added). As

Dr. Soiffer explains, Dr. Kahl's paper is not an anomaly—DLCL patients who may not be chemosensitive can and often do go through transplantation, and they did so before 1999. To be sure, the efficacy rate may be lower in that patient population, but even moderate success rates in treating a terminal illness such as DLCL can make a life-or-death difference. Ex. 1035 ¶¶ 32, 35.

Alternatively, as Dr. Soiffer explains, a POSA could have assessed sensitivity to CHOP by using CHOP alone for the first cycle(s), adding rituximab only in cycles two, three and/or four. *Id.* ¶ 35 n.2. As Dr. Kahl testified, chemosensitivity "would have been established by the third [dose]." Ex. 1034, 120:25. This slightly modified protocol, alone, would have resolved Patent Owner's chemosensitivity concerns.

In the end, none of Patent Owner's arguments rise to the level of showing that the prior art taught away from the claimed therapy, despite the motivation in the prior art to practice it. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be ***discouraged*** from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (emphasis added). The Federal Circuit explained in *Gurley* that even if the prior art suggested that one particular therapy might be inferior to another—say, because it had more toxicity—that does not mean that therapy becomes patentable. "A known or obvious composition does not become patentable simply because it has been

described as somewhat inferior to some other product for the same use." *Id.* Yet that is exactly what Patent Owner is arguing. The Board should reject those arguments as a matter of law, as well as on the evidentiary record.

III. CONCLUSION

For all these reasons and for the reasons stated in the Petition, Petitioner respectfully requests that the Board cancel claims 1–5 of the '873 patent.

Dated: May 24, 2018

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

Pursuant to 37 C.F.R. § 42.24, I certify that the foregoing PETITIONER'S REPLY TO PATENT OWNER RESPONSE contains 5,527 words (as calculated by the word processing system used to prepare the Petition), excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

Dated: May 24, 2018

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I certify that, on May 24, 2018, I caused to be served true and correct copies of the foregoing "PETITIONER'S REPLY TO PATENT OWNER RESPONSE," by electronic mail on the following attorneys:

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