**No. 19-1364**

In the

# United States Court of Appeals

## For the Federal Circuit

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BIOGEN, INC.,

*Appellant,*

v.

ANDREI IANCU, Director, U.S. Patent and Trademark Office,

*Intervenor.*

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ON APPEAL FROM THE U.S. PATENT AND TRADEMARK OFFICE
Case No. IPR2017-01168

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**APPELLANT'S REPLY BRIEF**

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## INTRODUCTION

The Intervenor does not dispute several key facts. All the evidence below indicated that a POSA[1] would not have combined all three treatments together without evidence that combining any two of the treatments was better than either treatment individually. None of the five cited prior art references reported results from any study that compared a two-treatment combination to either treatment individually. The Intervenor does not dispute these points. Rather, both the Intervenor and the Board mistakenly assume, contrary to the undisputed evidence, that a POSA would have combined all three treatments together simply because each was individually known in the art. As such, the Board's motivation-to-combine determination lacks substantial evidence.

Likewise, both sides' experts agreed that success in the context of the claims meant improving patient prognoses for DLCL patients over the age of 60. The Intervenor does not dispute this evidence. Instead, the Intervenor tries to defend the Board's reasonable-expectation-of-success determination by relying on a single, conclusory statement in Pfizer's expert report. That

[1] "POSA" refers to a Person of Ordinary Skill in the Art at the time of the invention claimed in the '873 patent.

reliance on conclusory testimony was legally improper and evidentially deficient. The Intervenor does not (and cannot) identify any non-conclusory testimony in the record to support the Board's ruling because no such evidence exists. The Intervenor also tries to salvage the Board's decision by contending that the claims do not require improved prognoses. But as a factual matter, it is undisputed that a POSA would have tied an expectation of success to improved prognoses, and none of the five cited prior art references disclose *any* improved prognosis. Therefore, the Board's reasonable-expectation-of-success determination lacks substantial evidence.

Intervenor also does not dispute that the Board failed to consider the motivation to combine and reasonable expectation of success from the POSA's viewpoint. By ignoring the expert testimony on the POSA's background knowledge, the Board improperly viewed the prior art without considering the POSA's point of view. That legal error merits reversal, and the Intervenor does not address or otherwise challenge that point in his brief.

The Intervenor likewise does not address that several of the cited references are fundamentally inapposite. The Intervenor concedes that when treating lymphoma patients, age and type of lymphoma were recognized as *the* critical prognostic factors to consider. Yet some of the

references on which the Board relied studied patients significantly younger than 60 or patients with less aggressive lymphomas than DLCL. The Intervenor devotes scant attention in his brief to these deficiencies in the prior art. Because those references did not study or report positive results of any kind for the claimed patient population, they would not have inspired in a POSA a reasonable expectation of success for treating DLCL patients over 60.

Because the Board disregarded the POSA's perspective and its ruling lacks substantial evidence, the Court should reverse and hold that the challenged claims are not obvious.

## ARGUMENT

### I. A POSA would not have been motivated to combine the prior art to make the claimed invention.

A POSA would not have been motivated to combine the prior art to arrive at the claimed triple-treatment combination because the record lacks evidence showing that any two-treatment sub-combination was better than either treatment individually. The Intervenor does not address what motivated a POSA, and instead views the prior art in a vacuum, divorced from the concerns of a POSA. That framing violates the bedrock rule that

the Board must consider the prior art "from the viewpoint of a person of ordinary skill in the field of the invention." *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 956 (Fed. Cir. 1997). Like the Board, the Intervenor assumes that a POSA *would* have combined the three treatments together simply because he *could* have. That gets the inquiry precisely backward: "[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art." *Belden Inc. v. Berk–Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015). Because the record lacks any evidence that a two-treatment combination was better than either treatment individually, there was no motivation to combine.

### A. A POSA would not have combined all three treatments together without evidence that any two of the treatments were better in combination than either one individually.

Both parties' experts agreed what would have motivated a POSA, and the Intervenor does not dispute this. Biogen's expert, Dr. Kahl, explained that "as of the priority date in August 1999, no two of those therapies [CHOP, rituximab, and stem cell transplantation] had been shown to be better together than each alone." Appx1125, ¶116. A POSA would not have combined all three therapies at once because "more testing was needed to

determine whether administering any two of CHOP chemotherapy, an anti-CD20 antibody, and a stem cell transplantation regimen was more effective (and still safe) as compared to each treatment alone." Appx1126, ¶118.

Pfizer's expert, Dr. Ozer, provided similar testimony. He explained that if a two-treatment combination improved on individual treatments, then researchers would "add[] another drug to that combination to see if the triple combination would be more effective." Appx987, 27:7–11. But "if more testing was needed" to see if the combination therapy "was more effective and still safe, then a person of ordinary skill in the art would test the combination therapy further *before trying to add a third drug*." Appx987, 27:12–18 (emphasis added).

The Intervenor also does not dispute that a POSA considered toxicity before combining treatments. For example, Pfizer's expert, Dr. Ozer, agreed that CHOP was more toxic to patients over 60. Appx990–991, 30:15–31:1. Dr. Ozer also conceded that "stem cell transplantation was known to be potentially lethal." Appx998, 38:11–14. And Dr. Ozer agreed that "the total toxicity associated with using multiple drugs together can be too high even if the toxicities of those individual drugs do not overlap." Appx985, 25:15–19. Given the risk of increased toxicity, physicians sensibly would not

expose patients to a potentially lethal three-treatment regimen without some evidence that two of the treatments in combination were at least better than the treatments given individually.

The POSA's concerns about toxicity naturally flowed from his understanding of the available medical treatments. A POSA would not prescribe treatments in the abstract. Pfizer's expert, Dr. Ozer, agreed that "efficacy *and toxicity* were *the critical parameters* for designing a treatment regimen for DLCL patients over 60 years old." Appx1019, 59:16–19 (emphases added). A POSA thus always considered the balance between toxicity and efficacy in deciding whether to combine treatments that could be toxic—and even lethal—to patients older than 60.

The Intervenor disputes *none* of this evidence. Without acknowledging the underlying concerns that animated POSAs, the Intervenor simply matches the claim elements to the prior art. Intervenor Br. at 18–20. This focus on the references rather than the POSA's mindset ignores the rule that "[o]bviousness, like anticipation, requires courts to consider the perspective of the ordinary observer." *Int'l Seaway Trading Corp. v. Walgreens Corp.*, 589 F.3d 1233, 1243–44 (Fed. Cir. 2009). Viewing the prior art from the POSA's perspective requires consideration of the POSA's

concerns, proclivities, and background knowledge. As this Court has reiterated, "[a]n obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case," but turns on "the common sense of those skilled in the art." *Leapfrog Enterprises, Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1161 (Fed. Cir. 2007). A POSA's common sense here taught him to be cautious before adding a third treatment to the mix, risking unacceptable toxicity, if it was unclear whether a two-treatment sub-combination was any better than either treatment individually.

This Court has recognized that POSAs do not haphazardly combine treatments or drugs to make claimed inventions. In *In re Brimonidine Patent Litigation*, 643 F.3d 1366 (Fed. Cir. 2011), the Court cautioned against concluding that a POSA *would* prescribe drugs together simply because he *could* have done so. "Two ingredients might be therapeutically effective when used separately as part of an overall treatment regimen, yet be *incompatible or ineffective* when combined in a single solution." *Id*. at 1374 (emphasis added).

The Intervenor erroneously seeks to distinguish *Brimonidine.* The Intervenor contends that "[t]he prior art, here, in contrast, expressly teaches all combinations." Intervenor Br. at 26. That misses the point. *Brimonidine*

shows that consideration of whether combinations work well together matters to a POSA. All the experts here agreed that overlapping toxicities were a real concern, and that a POSA would not have added all three treatments together if no evidence showed that any two of those treatments worked better than each one alone. In evaluating the prior art, the Intervenor failed to consider what motivated a POSA *not* to combine treatments together.

Finally, the Intervenor wrongly cites *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286 (Fed. Cir. 2013). Intervenor Br. at 26. In *Allergan*, the Court found a motivation to combine because the cited reference "provides an *express* motivation to combine alpha$_2$-agonists and beta blockers," the only two elements in the asserted claim. *Allergan*, 726F.3d at 1291 (emphasis added). Here, by contrast, no prior art reference expressly suggested the combination of CHOP, rituximab, and stem cell transplantation in a single regimen. And the undisputed evidence here—unlike in *Allergan*—shows that a POSA would not have been motivated to combine all three treatments without evidence that any two-treatment combination was better than either treatment individually.

### B. No combination of the cited references motivated a POSA to make the claimed invention.

The Board relied on a five-reference combination to show that the challenged claims were obvious. Appx19–30. Considered both individually and together, the cited references would not have motivated a POSA to make the claimed invention.

***Moreau***: Moreau was a pilot study that examined the feasibility of using CHOP and stem cell transplantation as upfront therapy for DLCL patients older than 60. Appx265. The Intervenor does not dispute that Moreau did not compare CHOP plus transplantation to CHOP alone. Appx268. The Intervenor also does not dispute that Moreau did not test or discuss rituximab. Appx268. Both parties' experts agreed that Moreau did not show the tested combination treatment was better than either treatment individually. *See* Appx1259, 60:6–19 (Dr. Kahl deposition testimony); Appx1008, 48:12–15 (Dr. Ozer deposition testimony).

The Intervenor ignores Moreau's failure to compare the combination treatment to either treatment individually. The Intervenor claims that "Moreau undisputedly teaches all of the claim limitations except administering rituximab." Intervenor Br. at 18. The Intervenor asserts that

as a result, the other references would have motivated a POSA to "add[] rituximab to Moreau's method." Intervenor Br. at 19. That contention puts the cart before the horse because a POSA would add a third drug *only* if he knew that the two-treatment combination was better than either treatment individually. *See* Appx987, 27:12–18 (Dr. Ozer deposition testimony); *see also* Argument § I.A.

The Intervenor also wrongly treats Moreau as a single treatment. The Intervenor contends that CHOP plus stem cell transplantation was "in effect a single treatment option." Intervenor Br. at 22. But the Intervenor does not dispute that the experts agreed *CHOP alone* was the standard of care at the time. *See* Appx1284, 85:18–25 (Dr. Kahl agreeing that "CHOP was the standard of care"); Appx1750, 94:5–16 (Dr. Soiffer agreeing that "CHOP [was] the standard of care for DLCL" patients). Even Moreau stated that "the CHOP regimen" was "considered the *standard first-line treatment* in high-grade NHL." Appx267 (emphasis added). If CHOP by itself did not induce remission, then a POSA may have added a stem cell transplantation regimen as a *second*, additional treatment.

The Intervenor's claim still fails even if a POSA considered CHOP plus stem cell transplantation to be a single treatment. The undisputed evidence

shows that a POSA would not have added rituximab to Moreau's regimen without evidence that CHOP plus stem cell transplantation worked better than CHOP alone. *See* Argument § I.A. The Intervenor concedes that Moreau *did not show* CHOP plus transplantation was any better than CHOP alone. Appx265–268. Thus, even if a POSA considered Moreau's regimen to be a single treatment, a POSA would still not have been motivated to add rituximab to Moreau.

***Link***: Link reports the abstract for a small pilot study that examined 31 patients with intermediate- or high-grade lymphoma. Appx257. The patients received CHOP and a monoclonal antibody as upfront treatment. Appx257. The Intervenor does not dispute that Link did not compare the tested combination treatment to any treatment individually. Appx257. And even Pfizer conceded that "Link did not study patients over 60." Appx101.

As with Moreau, the Intervenor ignores Link's fundamental limitations. The Intervenor states that "Link thus teaches that administering rituximab with CHOP provides a tolerable and possibly more effective therapy . . . than CHOP alone." Intervenor Br. at 19. But Link did not study patients older than 60. As Biogen explained, and as the Intervenor does not dispute, the patient's age was crucial information that a POSA would have

used to design treatments and predict survival outcomes. *See* Opening Br. at 10–12. Link's failure to study patients older than 60 would have limited its utility to a POSA looking for treatment options for over-60 DLCL patients with increased risk of toxicity.

Link's speculation that CHOP plus rituximab may be more effective than CHOP alone would not have motivated a POSA to add a third treatment. A reference's "speculative and tentative disclosure of what *'might' or 'may'* lead to [the relevant result] does not sufficiently direct or instruct one of skill in th[e] art." *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1376 (Fed. Cir. 2011) (emphasis added); *see also Genzyme Corp. v. Dr. Reddy's Labs., Ltd.*, 716 F. App'x 1006, 1010 (Fed. Cir. 2017) (same). Notably, the Intervenor does not address *Star Scientific* or *Genzyme*, both of which reject his argument that the speculative disclosures here are enough.

***McNeil***: McNeil is a news article that reports mainly on the initiation of a clinical trial that compared "CHOP alone to CHOP plus the monoclonal antibody." Appx249. The Intervenor does not dispute that the trial had just begun and that McNeil did not report any results. Appx249; *see also* Appx1003, 43:18–21 (Dr. Ozer agreeing that McNeil did not provide results). McNeil thus did not provide a POSA with the critical information that might

supply a reason to combine: whether a two-treatment combination outperformed either treatment given individually.

The Intervenor does not address the lack of results in McNeil. Instead, the Intervenor claims that McNeil "teaches the combination [CHOP + rituximab] in that age group" of patients older than 60. Intervenor Br. at 19. Although McNeil reported on a clinical trial that sought to answer whether a combination treatment was better than CHOP, McNeil never reported the study's conclusion. Thus, as of the priority date, McNeil could not have motivated a POSA to combine CHOP, stem cell transplantation, and rituximab all at once.

***Maloney***: Maloney is a 20-patient micro-study that examined the efficacy of rituximab alone. Appx271. As Pfizer's expert, Dr. Ozer, admitted "none of the patients with intermediate or high grade lymphoma," including the two DLCL patients, "responded to the therapy" in Maloney. Appx1013, 53:15–25. Maloney thus did not motivate a POSA to combine *any other treatment* with rituximab because Maloney did not even show that rituximab itself led to positive treatment outcomes in DLCL patients. In discussing Maloney, Intervenor Br. at 20, the Intervenor does not once mention that the only DLCL patients in that study did not respond to rituximab treatment.

***Coiffier***: Coiffier studied the efficacy of rituixmab alone. Appx259–262. Though Coiffier suggested testing rituximab along with CHOP, it did not mention or discuss stem cell transplantation. Appx259–262. Coiffier also did not report treatment results for DLCL patients older than 60, and thus identified no positive responders as elderly DLCL patients. Appx259–262. Because Coiffier tested only a single treatment, it does not (and cannot) show that a two-treatment combination was more effective than either treatment individually.

As all experts testified, a POSA would not have tested a *three*-treatment combination without some evidence that a *two*-treatment combination was better than the treatments given individually. That central concern animated the "perspective of the ordinary observer." *Walgreens Corp.*, 589 F.3d at 1243–44. The Intervenor tries to show obviousness by establishing that all the elements were present in the prior art, without ever addressing *why* a POSA would have combined them. Intervenor Br. at 18–20. As this Court explained, "[e]vidence suggesting reasons to combine *cannot be viewed in a vacuum* apart from evidence suggesting reasons not to combine." *Arctic Cat Inc. v. Bombardier Recreational Prod. Inc.*, 876 F.3d 1350, 1363 (Fed. Cir. 2017) (emphasis added). The Intervenor never provides any explanation of why a

POSA supposedly would have combined the prior art to make the claimed invention, especially given the risk of increased toxicity.

Even on its own terms, the Intervenor's argument falls flat. The Intervenor contends that the challenged claims are obvious if only one reference motivated a POSA to add rituximab to Moreau's regimen. Intervenor Br. at 18–19. None of the references fit the bill:

- ***Link***: Link thus did not motivate a POSA to add rituximab to Moreau because it did not study patients over 60. Appx257; *see L.A. Biomedical Research Inst. v. Eli Lilly & Co.*, 849 F.3d 1049, 1065 (Fed. Cir. 2017) (holding that prior art that did not study the relevant patient population did not supply a motivation to combine); *see also* Appx1768, 112:22–25 (Pfizer's expert, Dr. Soiffer, stating in deposition that "[i]f you looked at all patients over 60 versus all patients under 60, *both response and tolerability of treatment* would be different between those groups" (emphasis added)).

- ***McNeil***: McNeil did not report results from the study comparing CHOP alone to CHOP plus rituximab. Appx 249. McNeil thus did not motivate a POSA to add rituximab to Moreau because it did not show that CHOP plus rituximab was better than CHOP alone (or rituximab alone).

- ***Maloney***: The only DLCL patients in Maloney did not respond to the rituximab treatment. Appx273. Maloney thus did not motivate a POSA to add rituximab to Moreau because it did not report positive results for the claimed patient population—DLCL patients over 60.

- ***Coiffier***: Coiffier tested only rituximab, and did not report that any positive responder was a DLCL patient over 60. Appx263. Coiffier

> thus did not motivate a POSA to add rituximab to Moreau to treat DLCL patients over 60.

Even when considered as a whole, the references would not have motivated a POSA to make the claimed invention. No combination of the references provides results from any study that compared a two-treatment combination to either treatment individually, and the Intervenor does not claim otherwise. Because no subset of the cited references addressed that critical evidence, no combination of the prior art could have filled the gap. And without that evidence, a POSA would not have been motivated to combine the prior art to make the claimed three-treatment combination.

**C. The Board's findings lack substantial evidence.**

The Board found a motivation to combine the prior art only by disregarding the undisputed evidence on what motivated a POSA. That determination lacks substantial evidence.

The Intervenor mistakenly contends that CHOP plus stem cell transplantation was the "conventional therapy" for treating lymphoma as of the priority date. Intervenor Br. at 22. Yet as explained above, *supra* at 10, CHOP alone—not CHOP plus stem cell transplantation—was the standard of care for DLCL patients at that time. And while the '873 patent discusses

chemotherapy plus stem cell transplantation, it nowhere states that physicians used stem cell transplantation to treat DLCL patients *over 60*. Moreau makes that plain, as it notes that stem cell transplantation "is usually restricted to patients aged ≤60 years, partly due to the anticipated *poor tolerance of intensive treatment* in elderly patients." Appx265 (emphasis added). It therefore was not conventional as of the priority date to use CHOP plus stem cell transplantation to treat DLCL patients over 60.

The Intervenor ignores the POSA's perspective in summarizing the prior art. Intervenor Br. at 22–23. The Intervenor claims that Moreau taught two of the three treatments in the target patient population, and that the other references motivated a POSA to add rituximab to Moreau's regimen. "An invention is not obvious simply because all of the claimed limitations were known in the prior art at the time of the invention. Instead, we ask whether there is a *reason, suggestion, or motivation* in the prior art that would lead one of ordinary skill in the art to combine the references." *Forest Labs., LLC v. Sigmapharm Labs., LLC*, 918 F.3d 928, 934 (Fed. Cir. 2019) (emphasis added). The Intervenor does not discuss *why* a POSA supposedly would have combined all three treatments at once given (i) the risk of toxicity and

(ii) the lack of evidence showing a two-treatment combination as superior to either treatment individually.

The Intervenor wrongly claims that Biogen demanded evidence from clinical trials. Intervenor Br. at 24 n.8. Not so. Instead, Biogen focused on "evidence" in any form suggesting that a combination treatment worked better than either treatment individually. The Intervenor does not dispute that *no reference* reported results from a study that compared a combination treatment to a monotherapy.

The Intervenor tries to defend the Board's consideration of chemosensitivity by claiming that Pfizer's expert testimony "did not contradict the evidence cited by Biogen's expert." Intervenor Br. at 24. But the experts *disagreed* on whether chemosensitivity concerns discouraged a POSA from combining all three treatments in one regimen. *See* Appx1103–1105, ¶¶45–48 (Biogen's expert, Dr. Kahl, stating that chemosensitivity discouraged a POSA from adding rituximab to CHOP); Appx1386–1389, ¶¶32–35 (Pfizer's expert, Dr. Soiffer, asserting that chemosensitivity would not have discouraged a POSA). Though the Board credited Dr. Soiffer's testimony, his assertion of "general scientific knowledge[] require[s] support by documentary evidence in order to receive probative weight." *Upjohn Co.*

*v. Mova Pharm. Corp.*, 225 F.3d 1306, 1311 (Fed. Cir. 2000). The Board erred in treating this dispute as one about credibility because Dr. Soiffer did not supply *any evidence* to support his testimony on chemosensitivity. *See id.* at 1311 ("[T]here must be factual support for an expert's conclusory opinion."). Though Biogen cited *Upjohn* in its opening brief, the Intervenor does not address that case.

The Intervenor wrongly contends that toxicity would not have stopped a POSA from making the claimed invention. Intervenor Br. at 25–26. No reference compared the toxicity of a combination of treatments directly to the toxicity of either constituent treatment given individually. The record evidence highlights that the uncertainty over the toxicity of all three treatments combined weighed against combining them in one regimen:

- A leading international study of prognostic indicators for lymphoma found that patients over 60 were more susceptible to certain drug toxicities. Appx1106, ¶50.

- Pfizer's expert, Dr. Ozer, admitted "the total toxicity associated with using multiple drugs together can be too high even if the toxicities of those individual drugs do not overlap." Appx985, 25:15–19.

- Dr. Ozer also conceded that "using multiple therapies together can result in an unacceptable total level of toxicity." Appx984, 24:15–18.

At bottom, both the Intervenor and the Board ignored what actually motivated a POSA to combine treatments. All experts agreed that a POSA would not have combined all three treatments "if more testing was needed" to see if the combination therapy "was more effective and still safe" than either treatment individually. Appx987, 27:12–18. Because the Board's decision ignored the uncontroverted testimony on what motivated a POSA, its decision "r[an] counter to the evidence before the agency" and thus lacked substantial evidence. *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm*, 463 U.S. 29, 43 (1983).

## II. As of the priority date, A POSA would not have had a reasonable expectation of success in treating DLCL patients over 60 with the claimed invention.

A POSA also lacked a reasonable expectation of success because the prior art did not suggest that any combination treatment improved the prognoses of DLCL patients over 60. Again, both the Intervenor and the Board ignore the uncontroverted expert testimony on what "success" meant to a POSA. Instead, the Intervenor put a thumb on the scale towards invalidation by defining success as merely the absence of toxicity. But

because the experts here tied a reasonable expectation of success to improved patient prognoses, the lack of that evidence in the prior art underscores that the challenged claims are not obvious.

### A. All experts agreed that a reasonable expectation of success required evidence that a combination therapy improved the prognoses of DLCL patients older than 60.

The '873 patent explained that as of the priority date, physicians were looking to improve the prognoses of lymphoma patients. The patent states that POSAs were researching "alternative therapies" that "circumvent some of the deficiencies associated with current treatments and *decrease the frequency of relapse*." Appx53, 2:8–12 (emphasis added). Pfizer likewise described the problem facing a POSA as "whether new therapies *would have improved prognosis* for patients over 60 years." Appx120 (emphasis added).

All the expert testimony before the Board established that a reasonable expectation of success meant improving the prognoses of DLCL patients over 60. Biogen's expert, Dr. Kahl, explained that "[i]n this context I think success would mean that the treatment is proven to be better than what is already available." Appx1257, 58:1–4; *see also* Appx1257, 58:21–24 (Dr. Kahl stating during deposition that "my definition of success would mean that

the outcome was improved over what would have been achieved with a standard approach").

Likewise, Pfizer's expert, Dr. Soiffer, also linked reasonable expectations of success to improved prognoses. Dr. Soiffer agreed that head-to-head clinical studies "are necessary to show whether a novel therapy . . . ha[s] *better outcomes* than the standard of care." Appx1704, 48:4–9 (emphasis added). Dr. Soiffer therefore explained that "if we just talk about patients over the age of 60, successful treatment would mean *improving the prognosis* for patients over the age of 60." Appx1786, 130:10–19 (emphasis added).

The Intervenor does not dispute that none of the references provided a reasonable expectation of improving patient prognoses. As explained, none of the prior art reported results from a study that compared a two-treatment combination to either treatment individually. *See* Argument § I.B. The prior art thus did not contain evidence that *any* treatment combination improved patient prognoses, let alone that a three-treatment combination could improve patient prognoses without unacceptably increasing toxicity.

The Intervenor does not address the expert testimony below. Instead, he contends that a POSA would have successfully added rituximab to Moreau's regimen because Moreau discloses "no toxic deaths or severe

organ toxicity." Intervenor Br. at 20–21. That is not the benchmark for success in this context. Based on the patent's specification, consistent expert testimony, and Pfizer's own admission, a reasonable expectation of success here meant improving patient prognoses.

Even if the observed toxicities (or lack thereof) in Moreau were relevant, they still do not demonstrate a reasonable expectation of success. Moreau did not study rituximab individually or as part of a combination treatment. Appx268. As a result, Moreau did not provide evidence that a POSA could have safely added rituximab to CHOP plus stem cell transplantation. As Pfizer's own expert, Dr. Ozer, explained, "the total toxicity associated with using multiple drugs together can be too high even if the toxicities of those individual drugs do not overlap." Appx985, 25:15–19. The reported adverse events from Moreau's *two*-treatment study did not provide evidence that a POSA could have successfully combined *all three treatments* together with no unacceptable risk of toxicity.

Finally, the Intervenor's repeated references to the "predictable use" of the claim elements ignore the record testimony. Intervenor Br. at 11, 18, 20. The administration of CHOP, rituximab, or stem cell transplantation to treat aggressive lymphomas was not a simple exercise. This Court has

recognized that "in the medical arts[,] potential solutions are less likely to be genuinely predictable." *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. Inc., USA*, 748 F.3d 1354, 1360 (Fed. Cir. 2014). Indeed, Pfizer's own expert, Dr. Ozer, several times confirmed that potential therapies "often have negative results in clinical trials." Appx986, 26:15–18. Thus, contrary to the Intervenor's contentions, there was nothing predictable about combining together three intensive treatments that had not been combined before to treat aggressive forms of cancer in a fragile patient population.

**B. The Board's findings lack substantial evidence.**

The Board erred in finding a reasonable expectation of success, and the Intervenor does not show otherwise. The Board's chief error was relying on conclusory expert testimony. Pfizer's expert, Dr. Ozer, mentioned the expectation of success exactly once—at the end of a paragraph addressing motivation to combine. Appx193, ¶89. The Board supported its analysis of the reasonable expectation of success by citing only Dr. Ozer's conclusory assertion. *See* Appx30 (citing ¶89 of Dr. Ozer's declaration). The Board's reliance on conclusory testimony was legally impermissible. *Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1286 (Fed. Cir. 2017) ("As we

have stated, obviousness determinations cannot be sustained by merely conclusory statements.").

The Intervenor does not meaningfully address the Board's reliance on conclusory testimony. The Intervenor tries to rehabilitate Dr. Ozer's testimony, Intervenor Br. at 29, but all he said was:

> "[A] POSA would have found it obvious to combine the teachings of Link and Moreau to arrive at the invention of claim 1—the method of using rituximab and CHOP in combination with stem cell transplantation to treat patients over 60 years old with DLCL—and would have had a reasonable expectation of success."

Appx193, ¶89. The Intervenor does not explain how this conclusory expert testimony could have supported the Board's ruling.[2] *Cf. Wasica Fin. GmbH, Inc.*, 853 F.3d at 1286. Nor can the Intervenor save the Board's ruling by citing Dr. Soiffer's throwaway conclusion when discussing Coiffier. Intervenor Br. at 30; *see* Appx1383–1384, ¶27 (stating that "in view of

[2] Nor did Dr. Ozer's statement match the Board's reasoning. The Board found a reasonable expectation of success based on the cited five-reference combination. Appx30. But Dr. Ozer's conclusory statement referred only to Moreau and Link. His statement, therefore, did not show that a POSA would have had a reasonable expectation of success in combining all *five* references.

Coiffier," a POSA "would have reasonably expected successful outcomes in treating DLCL patients over 60").

The Intervenor wrongly accuses Biogen of relying on "snippets of [expert] testimony unconnected to the claim language" in addressing the reasonable expectation of success. Intervenor Br. at 29–30. But "[t]he presence or absence of a reasonable expectation of success is a *question of fact*" intertwined with expert testimony. *UCB, Inc. v. Accord Healthcare, Inc.*, 890 F.3d 1313, 1326 (Fed. Cir. 2018) (emphasis added). This Court often resolves the reasonable expectation of success by relying on expert testimony. *See, e.g.*, *Purdue Pharma L.P. v. Depomed, Inc.*, 643 F. App'x 960, 966 (Fed. Cir. 2016) (affirming Board's finding of no reasonable expectation of success given "both parties' experts testi[mony]"); *UCB Inc.*, 890 F.3d at 1326 (affirming finding of no reasonable expectation of success given the "expert testimony presented at trial" because "[w]e cannot reweigh the evidence, make credibility findings, or find facts"); *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1370 (Fed. Cir. 2012) (same).

The Intervenor cites no case law that justifies ignoring probative expert testimony when considering the reasonable expectation of success. Nor could he, as whether a POSA reasonably expected success turns on the

POSA's knowledge of the background art. *See UCB, Inc.*, 890 F.3d at 1326. And here, both Biogen's and Pfizer's experts explained that success meant improving patient prognoses for DLCL patients over 60. *See* Argument § II.A.

The Intervenor wrongly faults Biogen for considering the references individually rather than as a whole. Intervenor Br. at 30. As explained, the Board should not have considered several references *at all* because they either (i) did not study patients older than 60, or (ii) did not report positive treatment results for DLCL patients. *See* Opening Br. at 10–12, 51–53. And even if all five references were relevant, not one of them reported results from a study that compared patient prognoses between a combination treatment and an individual therapy. Therefore, the references, in combination, do not support the Board's findings.

Finally, the Intervenor fails to distinguish *Pozen Inc. v. Par Pharmaceuticals*, 696 F.3d 1151 (Fed. Cir. 2012). In *Pozen*, the Court held the claims were not obvious over the prior art partly because the art did not "disclose the combination therapy *has any added benefits* over any of the components given individually." *Id.* at 1163 (emphasis added). The Intervenor contends that unlike in *Pozen*, the claims here "do[] not recite any

added benefit over any single therapy." Intervenor Br. at 27. Yet, while the claims here do not expressly require enhanced efficacy, *all* experts tied a reasonable expectation of success to improved prognoses. *Pozen* teaches that when the relevant evidence calls for consideration of improved efficacy of treatment, the Board must consider it when evaluating obviousness. Because the Board did not, its finding lacks substantial evidence.

## III. The Board erred in finding claim 4 obvious because the prior art did not disclose treatment outcomes for DLCL patients over 60 with bone marrow involvement.

Claim 4 recites the method of claim 1 "wherein the lymphoma is accompanied by bone marrow involvement." Appx56, 8:49–50. Claim 4 is not obvious for all the reasons discussed above. *See* Argument §§ I–II. Separately, only two references addressed any patients with bone marrow involvement, and neither one would have motivated a POSA to create the invention described in claim 4.

Maloney provides no motivation to combine because it did not report positive results for the claimed patient population. While Maloney reported that some patients showed tumor responses in "bone marrow," none were DLCL patients. Appx271. Pfizer's own expert, Dr. Ozer, conceded that "none of the patients with intermediate or high grade lymphoma," including

the two DLCL patients, "responded to the therapy" in Maloney. Appx1013, 53:15–25. Thus, Maloney contains no evidence that a POSA could use rituximab (let alone any combination treatment including rituximab) to treat DLCL patients over 60 with bone marrow involvement.

Coiffier suffers from the same flaw. Coiffer treated patients with rituximab alone. Appx260. Only seven of the 52 patients in Coiffier had bone marrow involvement, and only three of those patients responded to treatment. Appx260. Coiffier did not report the age of the bone-marrow responders or whether they had DLCL. Appx260. A POSA reading Coiffier thus would not have known whether DLCL patients over 60 with bone marrow involvement responded positively to rituximab by itself, let alone to any combination treatment.

The Intervenor erroneously responds that Coiffier and Maloney would have motivated a POSA because bone marrow patients did not receive special treatments. Intervenor Br. at 30–31. That is irrelevant. Claim 4—like the other claims in the '873 patent—describes a treatment for *DLCL patients older than 60*. All experts agreed that age and type of lymphoma were critical prognostic factors to consider in designing treatment regimens as of the priority date. *See* Opening Br. at 10–12. Neither Maloney nor Coiffier

identified any positive responders as DLCL patients older than 60. Thus, even putting aside the dearth of evidence on patients with bone marrow involvement, neither Maloney nor Coiffier would have motivated a POSA to treat the target patient population with the claimed three-treatment combination.

## CONCLUSION

Because the Board failed to articulate a sufficient rationale for why a POSA would have sought to combine the prior art, and erred in concluding that the claims of the '873 patent are obvious, this Court should reverse.

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Respectfully Submitted,

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## CERTIFICATE OF SERVICE

I certify that on June 27, 2019, I filed the foregoing with the Clerk of this Court using the CM/ECF System, which will send notice of such filing to all registered CM/ECF users.

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This brief complies with the type-volume limitation of Federal Circuit Rule 32(a) because:

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