UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.
Petitioner

v.

BIOGEN INC.
Patent Owner

Case No. IPR2017-01095
Patent No. 9,296,821

PETITIONER'S COMBINED REPLY IN SUPPORT OF ITS PETITION FOR INTER PARTES REVIEW

TABLE OF CONTENTS

Cases

Other Authorities

I. INTRODUCTION

The question of validity of the '821 patent turns on logical consistency and fairness. On numerous issues, Patent Owner ("PO") has been talking out of both sides of its mouth, taking one position to argue an early priority date, then contradicting that position to argue against obviousness. PO cannot have it both ways. A consistent application of the facts compels invalidation.

For instance, recognizing that the '202 application to which it claims priority never discloses the specific use of rituximab during CVP treatment, PO reiterates that CVP was a standard chemotherapy. (PO Response ("POR"), 60.) But faced with explicit suggestions in the art to combine rituximab with "standard chemotherapy," PO insists that a person of skill in the art ("POSA") would not have combined rituximab with CVP. (*Id.*, 25-26.)

PO similarly relies on the '202 application's discussion of a study using rituximab as maintenance therapy ***after*** CVP treatment to suggest that the inventors were in possession of the use of rituximab ***during*** CVP therapy. (*Id.*, 64.) Then it contradicts itself by insisting that a Patient Protocol for the same study is not relevant prior art because it only discloses maintenance therapy ***after*** CVP. (PO Supplemental Response ("POSR"), 11-12, n.4.)

As to the claim term "beneficial synergistic effect," this panel has already

recognized PO's contradictory positions. (Decision to Institute ("DI"), 26-27.) PO relies on the generic disclosure, "treatment with anti-CD20 antibody provides a beneficial synergistic effect when administered in combination with . . . chemotherapy," in arguing that the '202 application discloses a beneficial synergistic effect of rituximab and CVP. (POR, 61.) Yet PO then asserts that this general disclosure in the prior art does not render obvious the beneficial synergistic effect of rituximab and CVP. (*Id.*, 52-53.)

PO's contradictions can be reconciled by concluding that while the use of rituximab during CVP therapy to achieve a beneficial synergistic effect was obvious to a POSA by August 1998, the named inventors were not in possession of that claimed invention. Because the petitioned claims are only entitled to a priority date of June 15, 2012, all claims are invalid in view of Marcus. (Petition ("Pet."), 38-44; *infra* V.)

Even as of PO's asserted priority date of August 11, 1999, a POSA would have been motivated to combine rituximab with CVP to treat Low-Grade/Follicular Non-Hodgkin's Lymphoma ("LG/F-NHL") to achieve a beneficial synergistic effect. CVP, like CHOP, was a standard chemotherapy for LG/F-NHL; rituximab was a breakthrough therapy; and rituximab in combination with CHOP was known to provide a beneficial synergistic effect for patients. By 1998, PO's own expert Dr. McLaughlin encouraged combining rituximab with standard chemotherapy. (*See,*

e.g., Ex.2002, 001.) PO argues that the R-CHOP combination was so successful that it would have discouraged, rather than encouraged, a POSA to combine rituximab with other standard chemotherapies, like CVP. (POR, 25-26.) But obviousness does not require the claimed invention be the only, or even preferred, combination to establish a motivation to combine. *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004).

A POSA also had a reasonable expectation of success. A POSA knew by 1998 that rituximab was successful as a single-agent, that R-CHOP provided a beneficial synergistic effect in LG/F-NHL patients, and that CVP was an effective, less toxic alternative to CHOP. PO has failed to demonstrate unpredictability associated with combining rituximab and CVP. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[O]nly a reasonable expectation of success, not a guarantee, is needed."). PO's secondary considerations are unavailing, as they are supported by attorney argument alone and do not show R-CVP results were unexpected. The '821 patent is thus invalid.

II. THE CHALLENGED CLAIMS ARE NOT ENTITLED TO THE AUGUST 1999 PRIORITY DATE

The Board correctly determined that claims 4-6 are not entitled to the August 1999 priority date because the '202 application does not disclose the "once every 3 weeks for 8 doses" limitation. (DI, 11-13.) But contrary to the Board's initial

finding, the '202 application also does not disclose treating LG/F-NHL with rituximab ***during*** CVP therapy, a limitation of every claim of the '821 patent.

While PO continues to point to disconnected disclosures (without expert support), these disclosures do not satisfy the requirement for written description: *possession* of the claimed combination of rituximab ***during*** a ***CVP*** regimen, to provide a beneficial synergistic effect. *Novozymes A/S v. DuPont Nutrition Bioscis. APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013) ("While the 2000 application provides formal textual support for each individual limitation recited in the claims of the #23 patent, it nowhere describes the actual functioning, thermostable alpha-amylase variants that those limitations together define."). Having failed to describe administering rituximab ***during*** a ***CVP*** regimen (*see* Pet., 22-27; Ex.1002, ¶¶76-89), PO cannot now claim that it described a beneficial synergistic effect using that specific regimen. PO itself maintains that "merely throwing out possibilities for combinations of pharmaceutical products does not mean that such combinations will work." (POSR, 13.) Thus, it is not enough that claim 17 generically suggests administering rituximab during chemotherapy, that the specification discusses an ECOG study using rituximab as ***maintenance*** therapy ***after*** CVP,[1] or that the

[1] Dr. McLaughlin testified in deposition and his declaration that rituximab administered during chemotherapy was distinct from maintenance therapy.

specification refers generally to anti-CD20 antibody providing a beneficial synergistic effect in combination with chemotherapy. Notably, all of these disclosures were in the prior art. The failure of the specification to identify CVP among the chemotherapies it listed and the failure to identify CVP as a chemotherapy to be combined with rituximab for a beneficial synergistic effect lead to the inescapable conclusion that the inventors did not possess that claimed invention at the time the '202 application was filed. (*See* Ex.1002, ¶¶76-89.)

Regarding claims 4-6, PO claims that Dr. Lossos's testimony that "standard CVP therapy" was understood to be 6-8 cycles spaced 3 weeks apart, and Ex.2024's disclosure of CVP therapy given every 21 days for 8 courses can supplement the '202 application. (POR, 65-66.) But PO cannot use this testimony to overcome the lack of written description in the '202 application. To satisfy the written description requirement, PO must show "that one is 'in possession' of the invention by describing the invention, with all its claimed limitations, not that which makes it

---

(Ex.2030, 160:15-162:4; Ex.2029, ¶68.) PO has likewise argued that the very ECOG study it relies on to support written description does not constitute prior art evidence for "administering rituximab with CVP." (POSR, 11-12, n.4 ("[B]ut in that [ECOG] study, rituximab was given *after* the CVP regimen, not *during* a chemotherapeutic regimen consisting of CVP therapy.").)

obvious." (DI, 12 (citing *Lockwood v. Am. Airlines*, 107 F.3d 1565, 1572 (Fed. Cir. 1997)).)[2]

III. CLAIM CONSTRUCTION

The prior art discloses all claim limitations under the construction adopted by the Board's Institution Decision,[3] as explained below in Sections V and VI.B.2. Petitioner nevertheless respectfully submits that the Board erred in its construction of the term "beneficial synergistic effect" as requiring "greater beneficial effect than the additive effects of the uncombined therapies." (DI, 7.) The Board's institution construction is not the broadest reasonable interpretation because it contradicts a POSA's understanding of the term, as PO's expert testified. *Knowles Elecs. LLC v. Iancu*, 886 F.3d 1369, 1374 (Fed. Cir. 2018) ("[E]ven under the [broadest reasonable interpretation], the [Board's] construction cannot be divorced from the specification and the record evidence . . . and must be consistent

[2] The Board correctly concluded in the *Pfizer* IPR challenging this patent that the '202 application's disclosure of *weekly* rituximab dosing after standard CVP therapy does not support the "once every three weeks for eight doses" schedule of claims 4-6. *Pfizer, Inc. v. Biogen, Inc.*, IPR2018-00186, Paper 15, 12-13 (Jun. 14, 2018).

[3] There is no meaningful distinction for purposes of this IPR between the institution construction and PO's proposed construction. (*See* POR, 13-14.)

with the one that those skilled in the art would reach.").

Dr. McLaughlin testified that a POSA would have found the Board's construction too "stringent." (Ex.2030, 49:22-50:8.) Per Dr. McLaughlin, understanding of "synergy" in the field lacked "rigidity" and often included "sensitization" or "potentiation" of the effects of one treatment by another – consistent with the construction proposed by the Petitioner: "an improvement in clinical outcome." (Pet., 30-31; Ex.2030, 80:24-81:19.) Dr. McLaughlin testified that in the context of his 1998 prior art reference, he "use[d] the word 'synergy' with a looser definition than the board's." (Ex.2030, 80:1-10.) His definition of "synergy" at the time was "sensitization," and Dr. McLaughlin testified that "sometimes, for better or worse, those words were used interchangeably." (*Id.*, 80:11-13, 81:8-13.) He ultimately agreed that "sensitization means that you're potentiating the activity of a compound that already has an activity." (*Id.*, 81:14-19.) Again, this construction is consistent with Petitioner's construction that the beneficial effect must be synergistic in that the outcome is improved compared to one drug alone. (*See, e.g.,* Pet., 50 (R-CHOP "superior to CHOP therapy alone.").)

PO relies on specification language reciting "better than additive" in the context of an anti-CD20 antibody + cytokine embodiment, and prosecution history from related patents, (*see* POR, 14-15), but those uses need not be limiting in light of PO's other uses of "synergy." During prosecution, for example, Applicant

referred to an improvement in clinical outcome as meeting the definition of synergistic effect without reference to any better-than-additive effect, stating "[p]atients treated with R-CVP experienced median progression free survival (PFS) of 2.4 years compared with 1.4 years in patients treated with CVP only, demonstrating a beneficial synergistic effect in the patient." (Ex.1069, 120.) In another example, the specification refers to the results in Demidem 1997 (Ex.1079), which describe rituximab-based sensitization of cells to chemotherapy, as an example of "synergy." (Ex.1001, 12:57-59, 19:5-9; Pet., 64; Ex.1002, ¶¶68, 70.) Accordingly, the complete intrinsic record reveals that PO's statements equating "synergy" with "better than additive" effects do not meet the standard for claim scope disclaimer. *See Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1366–67 (Fed. Cir. 2012). Instead, the broadest reasonable interpretation of beneficial synergistic effect is an improvement in efficacy compared to one therapy alone.

A practical problem with the Board's construction is that it leads to absurd results in context. For example, the Overall Response Rate (ORR) for rituximab alone was 50% (Ex.1011, 003; Ex.1027, 007) and CVP alone was 57% (Ex.1005, 003). Thus, for R-CVP to have "beneficial synergistic effect," under PO's construction, the ORR for R-CVP would need to be greater than 107%, which is scientifically impossible, as Dr. McLaughlin conceded. (Ex.2030, 172:16-173:14.)

Viewed in the practical context of oncology clinical trials, the broadest reasonable interpretation of "beneficial synergistic effect" should be an improvement in clinical outcome.

IV. PUBLIC AVAILABILITY OF PRIOR ART

A. Czuczman, Foon, Dana, and Marcus Were All Publicly Available

PO's arguments that Czuczman, Foon, Dana and Marcus are not prior art (and hearsay) are baseless. (POR, 19.) First, PO's arguments are evidentiary, and if raised at all should be raised in a motion to exclude.[4] Second, Petitioner submitted library date-stamped copies of Marcus, Dana, and Czuczman obtained by third-party document services as requested by librarians directed by attorneys. (Ex.1005, 001; Ex.1008, 001; Ex.1011, 001.) Foon is a copy of a renowned textbook chapter.[5]

As to PO's baseless suggestion that Petitioner's library-stamped exhibits are not *bona fide* prior art, Petitioner has responded with the declaration of expert

[4] In response to PO's objections, Petitioner served supplemental evidence before PO filed its POR, and will introduce this evidence if PO files a motion to exclude.

[5] PO's hearsay objections to Czuczman, Dana, Marcus, and Foon are overcome by Fed. R. Evid. 803(16) (ancient documents) and/or 807 – these references on their faces contain sufficient evidence of publication to self-qualify as prior art publications; PO *waived* any authenticity objection to Marcus and Dana.

librarian Dr. Sylvia Hall-Ellis, based on her personal knowledge regarding cataloging, indexing, and public availability of records like the prior art in this case. (Ex.1303, ¶¶1-38.) Dr. Hall-Ellis determined that Foon is authentic and was indexed and searchable by subject in the widely used Online Computer Library Center database, which is the authoritative database used by academic libraries in the U.S., and publicly available from The University of Colorado library, no later than August 16, 1994. (*Id.*, ¶¶39-43.) Dr. Hall-Ellis likewise confirms that Dana, Czuczman, and Marcus are authentic, were indexed by subject for searching, and were publicly available in The University of Colorado library by April 21, 1993 (*id.*, ¶¶44-49), November 25, 1995 (*id.*, ¶¶50-55), and February 28, 2005 (*id.*, ¶¶56-61), respectively.[6]

[6] The evidence supporting Dr. Hall-Ellis' declaration is authentic and admissible. Machine-Readable Cataloging ("MARC") and Wayback-Machine exhibits are business records under Fed. R. Evid. 803(6). The MARC exhibits are also public records under FRE 803(8) and ancient documents under FRE 803(16) (except for the Marcus-associated records). They also fall under the Rule 807 hearsay exception because of the guarantees of trustworthiness outlined in the Hall-Ellis declaration (Ex.1303, ¶¶39-61), because they are the most probative evidence of the fact of public accessibility, and admitting them would serve the interests of justice.

B. IDEC 10-K/A Was Publicly Available

The Board previously concluded that the 10-K/A was not sufficiently accessible to qualify as prior art. Respectfully, this conclusion was in error. First, SEC filings have been recognized as prior art disclosures sought out by a POSA, because confining a POSA's view to academic literature does not represent the resourcefulness and breadth of view taken by a POSA. *See, e.g.*, *Apotex Inc. v. OSI Pharm., LLC*, IPR2016-01284, Paper 49 at 21 (P.T.A.B. Jan. 8, 2018) ("We find that an ordinary artisan would have looked to OSI's 10-K to determine what drugs and treatments pharmaceutical companies were working on at the time of invention."); *see also CFAD (Adroca) LLC v. Acorda Therapeutics, Inc.*, IPR2015-01853, Paper 13 at 7-8 (P.T.A.B. Mar. 11, 2016) (company's S-1 registration statement was a printed publication based on news publications that indicated the company had performed clinical trials with the claimed agent for treatment of the disease at issue.).

Second, Ex.1006 was publicly accessible. PO questions accessibility, catalog/indexing, and whether a POSA would have looked to the 10-K/A. (*See* POSR, 4-6.) But by mandatory operation of the SEC's EDGAR system, the 10-K/A was published and searchable – as further supported by the Hall-Ellis declaration. (Ex.1303, ¶¶62-69.) IDEC was *required* to publish the 10-K/A to the EDGAR system, this system was routinely searchable, and a POSA would have had no difficulty in accessing this information. (*Id.*, ¶¶64-65.) Further, as explained by

Dr. Lossos, IDEC issued press releases by December 1996 announcing its intention to combine rituximab with other anti-cancer treatments. (*See* Ex.1002, ¶61 (citing Ex.1051).) A POSA has presumed knowledge of all prior art, not just academic publications. *See Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986) (POSA "presumed to be aware of all the pertinent prior art."). IDEC's press releases and other scientific publications about the promise of rituximab were sufficient to motivate a POSA to seek IDEC company filings like Ex.1006 that reported planned uses of rituximab.

V. GROUND 1: CLAIMS 1-6 ARE ANTICIPATED BY MARCUS

PO cannot seriously dispute that Marcus discloses every element of claims 2, 3, 5, and 6. Because these claims are not entitled to the August 1999 priority date, Marcus is prior art and anticipates all claims.

Regarding claims 1 and 4, PO asserts that Petitioner failed to argue that Marcus demonstrates a "beneficial synergistic effect" under PO's claim construction. (POSR, 18-19.) Setting aside the fact that Petitioner could not have divined what PO's proposed construction would be, the fact that Marcus meets this claim limitation is supported by PO's own arguments. PO relies on a chart it used in prosecution to support its construction of "beneficial synergistic effect." (POR, 16-17.) That chart cites Marcus for its disclosure that R-CVP had a better than additive effect for time to progression (TTP), as patients treated with R-CVP had a

median TTP of 32 months, more than the sum of 15 months for CVP alone and 9 months for rituximab alone. (Ex.1005, 003-004; Pet., 41; Ex.1002, ¶71.) As the Petition and Dr. Lossos relied on the same TTP data as PO does for disclosure of "beneficial synergistic effect," Petitioner did not waive this argument, and Marcus discloses claims 1 and 4 under the Board's current construction. (Pet., 38, 41; Ex.1002, ¶71.) The Board also correctly noted in a related proceeding that "beneficial synergistic effect" is non-limiting as to claim 4 because the claim recites a specific regimen for rituximab, and refers to standard "CVP therapy." *Pfizer*, IPR2018-00186, Paper 15 at 6-7, 16. Thus, Marcus's disclosure of the same dosing regimen of rituximab with standard CVP therapy to treat LG/F-NHL is sufficient to anticipate claim 4.

Alternatively, under Petitioner's proposed construction ("an improvement in clinical outcome"), Marcus also disclosed clear improvements in clinical outcomes. (Pet., 38, 41.) Thus, regardless of the claim construction, the record evidence confirms that Marcus anticipates claims 1 and 4.[7]

[7] Ground 2 presents no unique issues compared to Ground 1 in that PO no longer disputes the disclosures of the '137 patent relied on by Petitioner, effectively conceding the Board's initial determination. (DI, 18-19.)

VI. GROUND 3: CLAIMS 1-3 ARE OBVIOUS OVER CZUCZMAN, FOON AND DANA WITH OR WITHOUT 10-K/A[8]

Based on Czuczman's teaching that R-CHOP was effective for LG/F-NHL, a POSA would have considered it obvious to combine rituximab with other chemotherapies. (Pet., 45-54 (Ground 3).) As shown by Foon and Dana, CVP was an obvious substitute chemotherapy for CHOP given that CVP has similar efficacy but less toxicity. (*Id.*, 47-48, 51-52.) PO fails to address Petitioner's obviousness analysis directly. Instead, PO raises multiple red herring arguments that fail to overcome the strong motivation to combine the teachings of the prior art and reasonable expectation of success of the R-CVP combination.

A. A POSA Was Motivated to Combine Rituximab with CVP Chemotherapy

1. A POSA Was Motivated to Combine Rituximab with Standard Chemotherapy

Contrary to PO's assertions, a POSA reading Czuczman would not have ceased to seek alternatives to R-CHOP. (POR, 24-25.) PO's argument is rooted in the incorrect view that a POSA would have been so satisfied with the success of R-

[8] Contrary to PO's assertion, the Board can still consider the grounds on their merits with or without 10-K/A. *SAS* requires the Board to institute on all grounds or none, but nothing in *SAS* prevents a Board from determining, as here, that only a subset of cited references are necessary to support an instituted ground.

CHOP that he would have abandoned pursuit of combinations of rituximab with other standard chemotherapies. But the Petition describes, and the Board recognized, independent and sufficient reasons for motivating a POSA to combine Czuczman, Foon, and Dana to use R-CVP to treat LG/F-NHL. (*See* Pet., 51-52; DI, 24-29; *see also* Pet., 13, 16.)[9] First, the prior art, including a reference by McLaughlin, expressly suggests combining rituximab with other standard chemotherapies to treat LG/F-NHL. (*See, e.g.,* Ex.2002, 001; Ex.1006, 013.) Second, in view of the known toxicity of doxorubicin, CVP, which lacks the doxorubicin component of CHOP, was a less toxic approach for LG/F-NHL patients. (Pet., 10; *infra* VI.A.2.) Third, combination therapies were not confined to one particular chemotherapy, thus, combining rituximab with other known chemotherapies would have been obvious. (*See* Ex.1008, 029.) Fourth, CVP was a known standard chemotherapy for treating LG/F-NHL (*id.*) – even Dr. McLaughlin used the standard CVP therapy to treat LG/F-NHL patients. (Ex.2030, 34:3-10, 35:5-23, 37:22-24; *see also* Ex.2027, 11:11-12:5.)[10] As the Board recognized, a

[9] PO argues there is no motivation to combine Czuczman, Foon, and Dana without the 10-K/A. (POR, 22-24.) However, as the Board concluded, the 10-K/A is not required to motivate a POSA to combine the references. (DI, 21-29.)

[10]Dr. McLaughlin published a study in 1991 in which low-grade lymphoma patients

POSA looking at Czuczman's success with R-CHOP in LG/F-NHL patients would have been motivated to seek an equally effective, less toxic option than CHOP. (Pet., 51-52; *see also* DI, 27.) PO's Response provides no basis to depart from the Board's conclusion that based on Czuczman, Foon, and Dana, a POSA would have been motivated to combine rituximab with CVP for LG/F-NHL.

Further, the prior art and Dr. McLaughlin's testimony show that Czuczman's R-CHOP results made it obvious to try combinations of rituximab with the finite set of other known chemotherapies. (*See* Ex.2030, 52:10-14 (about ten standard combination chemotherapies available); 72:12-73:5, 74:15-22 (explaining benefit of having multiple effective regimens to choose from)); *see also Praxair Distrib., Inc. v. Mallinckrodt Hosp. Prod. IP Ltd.*, 890 F.3d 1024, 1037 (Fed. Cir. 2018) ("Where the level of ordinary skill in the art is high, and the claim applies a known solution to a known problem, it is 'likely the product not of innovation but of ordinary skill and common sense.'") (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)).) Dr. McLaughlin expressly encouraged other combinations, and clinical trials combining rituximab with chemotherapy other than CHOP were underway by 1998. (Ex.2002, 001; Ex.2030, 17:6-12, 18:5-22.) Dr. McLaughlin himself pursued

---

received CVP with bleomycin - only patients having adverse prognostic features received CHOP instead of CVP. (*See* Ex.2030, 112:4-113:23; Ex.1203.)

a clinical trial combining another known chemotherapy, FND, with rituximab, even after learning of Czuczman's R-CHOP results. (*See* Ex.2030, 70:24-71:10, 110:17-21.)

2. CVP Was An Effective, Less Toxic Alternative to CHOP For Treating LG/F-NHL

A POSA would have known that CVP was a standard, equally effective but less toxic alternative to CHOP for treating LG/F-NHL. (*See* Pet., 9-10; *see also* Ex.2027, 62:10-17.) There is no dispute that Foon and Dana teach that CHOP and CVP provide equivalent benefit in terms of overall survival ("OS") to LG/F-NHL patients. (*See* POR, 4-5, 35-36; Ex.2029, ¶39.)

PO argues that a POSA would have ignored the equivalency in survival benefit between CVP and CHOP because of results in efficacy endpoints such as response rates or remission rates. (*See* POR, 25-26, 35-36.) PO's attempt to change the focus to response or remission rates is unfounded. Given the indolent, asymptomatic nature of the disease, a POSA would have considered survival to be a more appropriate endpoint than response or remission rates. (Pet., 6-7; Ex.1002, ¶37; *see also* Ex.2027, 71:24:73:5; Ex.1025, 003; Ex.1018, 040.) If not, CVP would not have remained a standard therapy for LG/F-NHL alongside CHOP. (*See*

Ex.2030, 37:22-24, 50:24-51:4; Ex.1002, ¶¶39-40, 44; Ex.2027, 50:17-25.)[11] Thus, a POSA would have properly focused on survival, observed that CVP has indistinguishable survival rates over CHOP, and been motivated to use CVP to treat LG/F-NHL, just as Dr. McLaughlin did. (Pet., 9-10, 51-52; Ex.2030, 112:4-113:20.)[12]

As explained in the Petition and by Dr. McLaughlin, a POSA would have understood that the toxicity of CHOP is associated primarily with its doxorubicin component. (Pet., 10; Ex.1002 ¶39; Ex.2030, 119:17-120:3, 121:17-122:12.) Indeed, Dr. McLaughlin himself switched a patient from CHOP-Bleo to CVP-Bleo

[11] Depending on the cooperative group, CVP and CHOP were considered common chemotherapies to treat LG/F-NHL by 1999, and the choice in large part was based on physician's preference. (*See* Ex.2027, 40:20-41:4, 51:5-51:25; 62:10-63:25.)

[12] PO mischaracterizes Dr. Lossos's testimony to imply researchers accepted slightly more toxic chemotherapies as a worthwhile tradeoff since results of R-CHOP were so favorable. (POR, 42, n.17.) PO fails to mention that Dr. Lossos's response was to a question asking him to (1) focus on drugs other than CVP, and (2) *expressly* set aside efficacy. (Ex.2027, 25:22-26:12.) A POSA would not have worked under such unrealistic assumptions—she would have considered both efficacy and toxicity. (*See* Ex.2030, 128:3-8.)

when the patient experienced an adverse event. (Ex.2030, 122:21-123:22; *see* Ex.1203, 004[13].) Dr. McLaughlin admitted CVP is less toxic than CHOP:

> **Q**: [Adding doxorubicin to CVP] increased the risk of cardiac toxicity compared to CVP, correct?
>
> **A**: Probably so…. CVP . . . can itself be associated with cardiac toxicity, but I think it's less than with CHOP."

(Ex.2030, 121:17-122:12; *see also* Ex.2027, 80:25-81:7.)

PO wrongly suggests that Czuczman, Foon, and Dana do not address the relative toxicities of CVP and CHOP. (POR, 38.) Foon and Dana call combination therapies like CHOP that contain doxorubicin "intensive" or "aggressive" combination regimens. (Ex.1008, 030; Ex.1009, 002.) In this context, "intensive" and "aggressive" mean toxic, because they mean either administering more frequent chemotherapy, more agents, or larger doses of agents, which all inevitably translate to increased toxicity risk. (Ex.2027, 57:17-58:13, 59:8-60:13.)

PO confuses the issues by arguing that a POSA would have believed "appropriate" efficacy against LG/F-NHL would require non-standard CVP regimens using increased doses of cyclophosphamide. (POR, 39.) This argument ignores the undisputed fact that CVP and CHOP were standard therapies known to have equivalent survival benefit for patients. (*See* Ex.1008, 029-030; Ex.1009, 006

[13] Petitioner's Exhibits 1203 and 1302 are authentic. (*See* Ex.1300.)

("addition of doxorubicin to CVP results in no improvement in survival.").) In that context, CVP is clearly less toxic. (Ex.1008, 030 (combination regimens including doxorubicin are "intensive" compared to CVP); Ex.1044, 004 (cited by Ex.1009 for CVP results); Ex.1002, ¶¶40-43.) PO's attempt to compare dosing of orally administered cyclophosphamide in CVP versus intravenously administered cyclophosphamide in CHOP also fails because differences in bioavailability with oral and intravenous administration make dose comparisons flawed. (*See* POR, 39-40; Ex.2027, 14:14:1-15:5; Ex.1008, 029.)

3. CVP Was the Most Appropriate Alternative to CHOP

PO argues that single-agent therapies, such as chlorambucil, cyclophosphamide, fludarabine, pentostatin, cladrabine, or other chemotherapies would have been better options than CVP for combination with rituximab. (POR, 36, 40-41.) However, as the Board recognized, it is enough that "Foon and Dana suggest that Petitioner's proposed modification of Czuczman amounts to a simple substitution of one known low grade NHL chemotherapy for another." (DI, 27); *see also Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1328 (Fed. Cir. 2017) ("obviousness 'does not require that the motivation be the *best* option, only that it be a *suitable* option from which the prior art did not teach away.'" (citation omitted)); *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (that the prior art teaches "a multitude of effective combinations does not

render any particular formulation less obvious. This is especially true because the claimed composition is used for the identical purpose taught by the prior art.").

Even under PO's misguided view of obviousness, CVP was the most reasonable alternative to CHOP given the close similarity of the two regimens' components and the favorable efficacy and toxicity profile obtained with CVP as compared to PO's alternatives. (*See, e.g.* Ex.2027, 24:14-27:3.) Dr. McLaughlin agreed that CVP was superior to chlorambucil. (Ex.2030, 138:14-19; Ex.2027, 90:4-18; *see also* POR, 33 (noting advantages of CVP over single-agent alkylating therapy, citing Ex.1008, 029-030).) Ultimately, it makes no sense for PO to argue that POSA would have been motivated to combine rituximab with every chemotherapy known to provide a benefit in LG/F-NHL *except* CVP. CVP was the most similar to CHOP and thus, the most appropriate substitute for CHOP in R-CHOP for LG/F-NHL.[14]

[14] McNeil's combination alternatives for CHOP, such as mini-CHOP, would not have negated a motivation to pursue CVP for LG/F-NHL. (*See* POR, 41.) McNeil discusses *intermediate-grade* NHL ("IG-NHL"). Because IG-NHL is more aggressive than LG/F-NHL, CHOP was preferred to CVP for that disease. (Pet., 9; Ex.1002, ¶39.) McNeil's alternatives to the "more toxic" CHOP in the context of IG-NHL would not have applied to LG/F-NHL.

Lastly, PO cites two other studies to imply that a POSA would have chosen other doxorubicin-containing regimens as alternatives to CHOP. (POR, 32, n.15.) As noted above, due to the toxicity associated with doxorubicin, doxorubicin-containing regimens were not suitable replacements. (Pet., 9-10; Ex.1002, ¶39; *see also* Ex.2030, 119:17-25.) Further, PO mischaracterizes the studies it relies on. PO argues that Ex.2025 reported "better 'failure-free survival'" with intensive regimens containing doxorubicin. (POR, 32, n.15.) In actuality, Ex.2025 concluded that "[s]urvival did not differ by either treatment [cyclophosphamide v. CAVBP]." (Ex.2025, 00003.)

4. The Prior Art Does Not Teach Away From Using R-CVP

a. Czuczman's Results Would Not Have Dissuaded POSA from Pursuing R-CVP

PO argues that given the remarkable results achieved with R-CHOP—100% response rate and conversion to *bcl*-2 negativity—a POSA would not have been motivated to replace CHOP. (POR, 25-26.) But nothing about the known benefit of combining rituximab with CHOP "teaches away" from the obvious combination of rituximab with CVP. *See Meiresonne v. Google, Inc.*, 849 F.3d 1379, 1382 (Fed. Cir. 2017) (prior art does not teach away if it "merely expresses a general preference for an alternative invention" but does not "discredit" or "discourage" the claimed invention). To the contrary, the prior art results with R-CHOP would have

encouraged POSA to expect similar successes in response and *bcl*-2 clearance endpoints.

A POSA would not have attributed the positive results obtained with R-CHOP specifically to CHOP. For example, Czuczman reported that R-CHOP patients successfully converted *bcl*-2 positive cells to *bcl*-2 negative cells. *Bcl*-2 negativity was known to be associated with improved patient outcomes. (Ex.1025, 004.) To that end, Czuczman teaches that CHOP alone was *unable* to clear *bcl*-2 positivity in marrow. (Ex.1011, 003.) And as McLaughlin reported in 1996, "*bcl*-2 [negativity]" was achieved "after treatment with [rituximab] as a [single agent]." (Ex.1302, 011.) In short, rituximab, *not* CHOP, was most likely responsible for the conversion from *bcl*-2 positivity to *bcl*-2 negativity as reported by Czuczman. (Ex.2030, 97:14-20, 103:4-7, 106:2-18; Ex.1048, 003.) A POSA would have had every reason to combine rituximab with CVP to achieve *bcl-2* clearance, and certainly would not have been discouraged from pursuing the combination.

b. Doxorubicin Offered No Particular Benefit that Would Have Discouraged POSA from Pursuing R-CVP

PO's assertion that POSA would not have replaced CHOP with CVP for fear of losing a "particular benefit" that doxorubicin yields with rituximab is baseless. (POR, 28.) First, PO never describes this alleged specific "benefit," but only generally cites several Czuczman publications without explanation. (*See* POR, 28

(citing Ex.1041, Ex.1011, Ex.1039).) Ultimately, PO cannot ignore Czuczman's express disclosure of rituximab's "synergy with chemotherapeutic agents"—which includes agents other than doxorubicin. (*See* Ex.1011, 003; Pet., 45-46.)

Even assuming that rituximab sensitizes tumor cells to doxorubicin, a POSA would have understood this phenomenon is not unique to doxorubicin, but instead would likely occur with "various cytotoxic drugs/toxins," including a component of CVP. (*See* Ex.1002, ¶¶68-70, explaining Demidem's findings.) A POSA had specific reason to expect rituximab-based sensitization to CVP because Demidem also showed rituximab sensitized cells to cisplatin, which was known to behave like an alkylating agent, and cyclophosphamide (a component of CVP) is an alkylating agent. (Ex.1002, ¶68; Ex.1079, 002; Ex.2030, 84:5-9, 85:20-23.) Dr. McLaughlin employed similar logic to explain that Demidem's disclosure of rituximab-based sensitization to doxorubicin was encouraging for rituximab-based sensitization to a similar compound, mitoxantrone. (Ex.2030, 86:10-88:1.) Further, Dr. McLaughlin admitted that the synergy described by Demidem and referred to by Czuczman is the "potentiation" to chemotherapy that rituximab effects in tumor cells. (Ex.2030, 81:8-19.) Accordingly, a POSA would not have attributed any of these supposed particular benefits to doxorubicin, but to rituximab itself.[15]

[15] Nor would a POSA have considered CHOP to be a "cure" for LG/F-NHL as POR

B. The Prior Art Provided Ample Expectation of Success

1. Success of R-CHOP Provided Reasonable Expectation of Success of R-CVP in LG/F-NHL Patients

The overwhelming weight of evidence supports a reasonable expectation of success in combining rituximab with CVP to treat LG/F-NHL patients. First, R-CHOP had provided "remarkable" results (with rituximab and not CHOP responsible for *bcl*-2 clearance). (POR, 8; *supra* VI.A.4.a.) Second, several prior art references, including Dr. McLaughlin's publication, encouraged combining rituximab with other chemotherapies. (Ex.1020, 009; Ex.1050, 003; Ex.2002, 001; Ex.1006, 013.) Dr. McLaughlin noted "[f]urther investigation of [rituximab] is warranted, including its use in conjunction with standard chemotherapy." (Ex.2002, 001.) Indeed, Dr. McLaughlin himself pursued combining rituximab with FND chemotherapy, even after learning of the success of R-CHOP. (Ex.2030, 18:5-10,

---

suggests, (POR, 26 (citing Exs. 1008 and 1059)), because the studies PO cites relate to Intermediate-Grade or High-Grade NHL. (*Id.*) As PO has previously argued, "a POSA would not have assumed that successful treatment of one grade of lymphoma would translate into successful treatment of a different grade." (Ex.1324, PO's Preliminary Response, *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01094, Paper 10 at 9 (P.T.A.B. Jul. 5, 2017).)

70:24-71:10, 110:17-21; *see also* Ex.2027, 19:17-20:10.) Third, CVP was a standard chemotherapy for LG/F-NHL with the same efficacy in treating LG/F-NHL as CHOP. (*See supra* VI.A.) Dr. McLaughlin conceded that the R-CVP combination was a "*worthy* hypothesis to test in a clinical trial." (Ex.2030, 146:15-148:12 (emphasis added).) In the absence of any suggestion that R-CVP would not work, the clinical trial testing this worthy hypothesis reflects the POSA's reasonable expectation of success. *Soft Gel Techs., Inc. v. Jarrow Formulas, Inc*., 864 F.3d 1334, 1342 (Fed. Cir. 2017) ("An incentive to conduct a confirmatory study frequently exists even when one has every reason to expect success."); *In re Merck & Co.*, 800 F.2d 1091, 1096 (Fed. Cir. 1986) (claims directed to a method of treating depression with amitriptyline were rejected as prima facie obvious based on research paper suggesting clinical testing of amitriptyline as an antidepressant.). Contrary to PO's assertion, obviousness does not require a guarantee that trials be successful. *Pfizer*, 480 F.3d at 1364 ("[O]nly a reasonable expectation of success, not a guarantee, is needed.").

PO's assertion that actual testing of R-CVP is required to establish reasonable expectation of success (POSR, 11, 13) is incorrect. *See Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness."); *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988) (in unpredictable field, obviousness showing requires a reasonable

expectation of success, not an actual reduction to practice). PO cites *Genzyme* (a non-precedential opinion) for its proposition that testing is required to prove reasonable expectation of success, but *Genzyme* is inapposite. (POSR, 11 (citing *Genzyme Corp. v. Dr. Reddy's Labs. Ltd.*, 716 F. App'x. 1006, 1010 (Fed. Cir. 2017).) In *Genzyme*, the court found no reasonable expectation of success because there was no explanation in the prior art for the hypothesis that the claimed agent, plerixafor, may cause stem cell mobilization, and there had never been *any* testing of the claimed agent or similar classes. *Genzyme*, 716 F. App'x. at 1010. By stark contrast here, (1) the express teachings of the prior art encouraged combining rituximab with other chemotherapies, (Ex.1011, 003) (2) CVP was an established, standard chemotherapy for LG/F-NHL, and (3) rituximab combined with an equally effective chemotherapy, CHOP, had been successful. Thus, the success of R-CVP was reasonably predictable. Finally, PO argues unpredictability based on Demidem's report that rituximab does not sensitize cells to the drug etoposide. (POSR, 13.) As etoposide is not a component of CVP, this argument is a *non sequitur*. A POSA would have focused on Demidem's broader conclusion that cells pretreated with rituximab "were found to be ***more sensitive to all cytotoxic agents tested***" except for etoposide. (Ex.1079, 006.) One of the other cytotoxic agents that Demidem reported synergized with rituximab was cisplatin, which acts through a mechanism of action similar to cyclophosphamide, the **C** component of **C**VP as

previously discussed. (*See supra*, VI.A.4.b). Accordingly, a POSA had a reasonable expectation that rituximab would synergize with CVP.

2. POSA Had a Reasonable Expectation of Success in Obtaining Beneficial Synergistic Effect with R-CVP

Czuczman provided a more than reasonable expectation that R-CVP would achieve a "better-than-additive" beneficial synergistic effect, particularly as to response rates and *bcl-2* conversion. (POR, 51-55.) Regarding response rate, R-CHOP was better than additive for Complete Responses (CR), where rituximab alone provides a CR of 6% (Ex.2002, 003), CHOP provides a CR of 18% (Ex.1047, 005; Ex.1002, ¶¶ 40, 109) and R-CHOP provides a CR of 63%. (Ex.1049, 003; *see also* Ex.1011, 003; Ex.1002, ¶¶40, 102.) Even for Overall Response, R-CHOP provided the maximum possible response, 100%, where rituximab provides an OR of 48% (Ex.2002, 003) and CHOP provides an OR of 60% (Ex.1047, 005). Czuczman thus showed that R-CHOP had a beneficial synergistic effect on response rates, even under the PO's construction of that term.

The R-CHOP results reported by Czuczman also provided a reasonable expectation of success to achieve better-than-additive *bcl-2* conversion. The prior art reported that *bcl-2* conversion occurred in no cases (or 0%) with CHOP (Ex.1041, 003) and 56% of cases with rituximab (Ex.2002, 005), while Czuczman reported R-CHOP *bcl-2* conversion in 100% of cases. (*See* Ex.1011, 003; Ex.1002, ¶104.)

Given this beneficial synergistic effect from R-CHOP, a POSA would have reasonably expected these same benefits for the combination of R with CVP.[16]

PO argues that Czuczman's express disclosure of "synergy with chemotherapeutic agents" does not reflect the actual findings of Czuczman, and was not a disclosure of clinical outcomes. (POR, 53.) But this contradicts PO's arguments in support of an August 1999 priority date. (POR, 61.) As the Board

[16] PO's objection to cross-study comparisons (POR, 47-49) does not undermine the existence of a reasonable expectation of success. PO has relied on cross-study comparisons when convenient. For example, Dr. McLaughlin confirmed he used a cross study comparison in paragraph 40 of his declaration. (*See* Ex.2030, 139:23-140:7.) And when it argued during prosecution that R-CVP provided a beneficial synergistic effect, PO relied on a table that uses cross-study comparisons. (*See* POR, 17, drawing data for rituximab, CVP, and R-CVP from Marcus and two McLaughlin studies (cited in Ex.1034, 022-023, 047).) In the absence of any single study that compares the treatments side by side (*see* Ex.2030, 166:25-167:8), a POSA had no option but to make cross-study comparisons. Evaluating the art that was available across different studies, a POSA would have concluded that Czuczman demonstrated synergy with R-CHOP and would have had a reasonable expectation of success in combining R with CVP.

recognized, "Patent Owner's synergy argument is not well-taken as it cuts against its argument raised in the context of whether the '202 application described the combination of rituximab and CVP as providing a beneficial synergistic effect." (DI, 26.) Particularly in view of the specific examples above of the greater beneficial effect that R-CHOP provided compared to the additive effects of the uncombined therapies, PO's argument fails.

To the extent PO would impose a requirement for express disclosure of detailed scientific data in the prior art (POR, 52-53, 55), that standard is incorrect. A POSA would have considered Czuczman "not only for what it expressly teaches, but also for what it fairly suggests." *In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994); *see also In re Inland Steel Co.,* 265 F.3d 1354, 1360-61 (Fed. Cir. 2001). Czuczman's teachings that rituximab exhibited "synergy with chemotherapeutic agents" and that "anti-tumor activity of CHOP and [rituximab] is superior to CHOP therapy alone" (Ex.1011, 003) would have suggested to a POSA that rituximab with chemotherapy had a clinical outcome resulting from combination therapy that reflects a greater beneficial effect than the additive effects of the uncombined therapies when administered alone. (Ex.1002, ¶¶57, 70, 111-112.) Indeed, the plain words of Czuczman, Ex.1041, state "[m]echanisms of action of [rituximab] include[s] . . . *synergistic antitumor activity* with certain chemotherapeutic agents." (Ex.1041, 003 (emphasis added).) In view of all of the above, a POSA would have

understood that Czuczman describes a "beneficial synergistic effect" even under the Board's construction.[17] (Pet., 50; Ex.1002, ¶¶103, 112.)

3. Clinical Endpoint Data for CVP and CHOP Supported a Reasonable Expectation of Success for R-CVP

PO's attempts to minimize the equivalent clinical outcomes reported for CVP and CHOP in arguing a lack of reasonable expectation of success are confusing and undermined by its own expert. (POR, 47-49.) PO seeks to discredit Dr. Lossos's factual support for the conclusion that, although CHOP is more aggressive than CVP, similar survival rates have been reported for the two regimens in LG/F-NHL patients, and CHOP and CVP were thus equally effective. (*Id.*; Ex.1002, ¶40.) In this context, PO rejects comparing results between different trials that studied CVP and CHOP. But neither expert found any prior art trial where CVP and CHOP were tested side by side. (Ex.2030, 146:9-18.) PO then argues that two studies, Kimby and Canellos, show CHOP has a higher CR rate at 60% than CVP at 50%, relying

[17] PO contorts Dr. Lossos's testimony, suggesting he believed *in vitro* data is required to determine synergy under the Board's construction (POR, 54). Dr. Lossos testified that POSA would generally have understood synergy to be quantified using experimental data with *in vitro* cell lines, and was not discussing the issue "under Board's construction." (Ex.2027, 32:1-14; *see also id.* 87:7-25.)

on the McLaughlin declaration. (POR, 48.) But Dr. McLaughlin retracted this statement in his deposition, acknowledging that CR for CHOP was actually reported by Kimby as 18%. (*See* Ex.2030, 139:10-12, 140:13-24.) Thus, the reported CR for CVP is 32% better than that reported for CHOP. These data further support the conclusion that a POSA understood generally the similarity of outcomes achieved by CVP and CHOP overall, and would reasonably have expected the R-CVP combination to be comparable to the R-CHOP combination.

4. Chemoimmunotherapy Using Rituximab Was Not Unpredictable by August 11, 1999

PO's contention that combining immunotherapy with chemotherapy was generally "uncertain" or "unpredictable" (POR, 28-30) is off-base because it ignores the breakthrough that rituximab embodied. PO argues that a POSA would not have expected success with R-CVP, relying on prior chemoimmunotherapies discussed in Foon rather than what was specifically known about rituximab. (POR, 28-30, 44; POSR, 10.) PO's arguments disingenuously focus on failed predecessor immunotherapies (INF-α, INF-β, IL-2, and anti-idiotype antibody) while ignoring the strong single agent activity of rituximab in LG/F-NHL patients (Ex.1032, 003; Ex.1021, 002). A POSA would have considered the significant results achieved with rituximab and would have been focused on the likelihood of success of rituximab with CVP, with the knowledge that rituximab was a special immunotherapy that had

enhanced activity when combined with CHOP. Unpredictability of alternative chemoimmunotherapies does not undercut the specific evidence for expectation of success with rituximab. *See Pfizer*, 480 F.3d at 1364-66 (evidence specific to formation of the specific claimed salt proved obviousness, even in light of general unpredictability of salt formation).

C. PO's Secondary Considerations Arguments Fail

PO has failed its burden of production to show existence of secondary considerations.[18] *Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1101-02 (Fed. Cir. 2015) (patentee has a production burden for secondary considerations evidence). PO advances only attorney arguments for unexpected results, with no additional evidentiary support. This is inadequate. *See Conopco, Inc. v. Procter & Gamble Co*., IPR2013-00505, Paper 69 at 27 (P.T.A.B. Feb. 10, 2015); *In re Soni*, 54 F.3d 746, 753 (Fed. Cir. 1995) ("[U]nexpected results must be established by factual evidence. Mere argument or conclusory statements . . . [do] not suffice.").

PO's unexpected results arguments are also legally unsound because PO fails to compare the claimed invention with the closest prior art. *In re Baxter Travenol*

[18] Dr. McLaughlin provided no opinions on secondary considerations. (Ex.2030, 45:3-5; *see* Ex.2029, ¶¶49-126.)

Labs., 952 F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art."); *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014); *Apotex*, IPR2016-01284, Paper 49 at 46. Here, the closest prior art is the compelling result of combining rituximab with CHOP (which contains all of the components of CVP). PO ignores this art, and compares R-CVP to results obtained with CVP alone. (POR, 68-69 (citing Ex.1069, 120-21).) When viewed against the results obtained with R-CHOP, a POSA would have expected R-CVP to be much more effective than CVP alone. This conclusion is especially strong here, where PO has provided *no* evidence of skepticism or teaching away regarding the supposedly unexpected results. Finally, PO's assertion that benefits of R-CVP were surprising in view of alleged "benefits" of doxorubicin—rituximab sensitization or achievement of minimal tumor burden—also fails because neither is specific to doxorubicin. (POR, 69-70; *see supra* VI.A.4.b.)

VII. GROUND 4: CLAIMS 4-6 ARE OBVIOUS OVER CZUCZMAN, FOON, DANA, LINK AND PIRO WITH OR WITHOUT 10-K/A

PO asserts that Petitioner has not explained why Link's dosing regimen to treat IG-NHL is appropriate for treating LG/F-NHL (POSR, 16-17), but during prosecution, Applicant relied on the same disclosure to argue that the '202 application provides support for administration of rituximab "once every three

weeks" for treating LG-/F-NHL patients. (Ex.1069, 186-87; Ex.1034, 040.) PO also relied on '202 application's description of treatment of a different NHL, mantle-cell lymphoma, to argue written description support for the "once every three weeks" administration in LG/F-NHL patients. (*See* POR, 65 (citing Ex.1034, 040).) While these disclosures were insufficient to demonstrate that the inventors were in possession of the dosing regimen at the time of filing, these disclosures would have rendered the claimed invention obvious. *Lockwood*, 107 F.3d at 1572.[19]

The Petition and Dr. Lossos explain that because the same chemotherapy combination as Link is described in Czuczman, a POSA would have found it obvious to optimize the therapy and use the once every 3 week dosing of rituximab when combined with CHOP or CVP. (Pet., 60-61; Ex.1002, ¶¶118-120.) Additionally, as Piro describes administering eight weekly doses of rituximab for treating LG-/F-NHL, a POSA would have found it obvious to modify the dosing regimen of Czuczman, Link, and Piro to administer rituximab once every 3 weeks for 8 doses. (*Id*.)

VIII. CONCLUSION

For the foregoing reasons and the reasons set forth in the Petition for *Inter*

[19] Ground 5 presents no unique issues compared to Ground 4. (*See supra* VI, n.7; DI, 19.)

Partes review, Petitioner respectfully requests claims 1-6 be canceled.

Dated: July 5, 2018

By: */Michelle S. Rhyu/*
Michelle S. Rhyu
(Reg. No. 41,268)
Counsel for Petitioner

Cooley LLP
Attn: Patent Docketing
1299 Pennsylvania Avenue NW
Suite 700
Washington D.C. 20004
Tele: 650-843-5505
Fax: 650-849-7400

CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PETITIONER'S COMBINED REPLY IN SUPPORT OF PETITION FOR INTER PARTES REVIEW complies with the type-volume limitation in Paper 40 at 4. According to word count function of the word processing system used to prepare this brief, the brief contains 7,600 words, excluding parts of the brief exempted by 37 C.F.R. § 42.24(a)(1).

Date: July 5, 2018

/Michelle S. Rhyu/
Michelle S. Rhyu
Reg. No. 41,268
Counsel for Petitioner

Cooley LLP
Attn: Patent Docketing
1299 Pennsylvania Avenue NW
Suite 700
Washington D.C. 20004
Tele: 650-843-5505
Fax: 650-849-7400

CERTIFICATE OF SERVICE

I, Michelle S. Rhyu, hereby certify that on this 5th day of July 2018, the foregoing PETITIONER'S COMBINED REPLY IN SUPPORT OF PETITION FOR INTER PARTES REVIEW was served via electronic mail on the following:

IRELL & MANELLA LLP
Michael R. Fleming
Gary N. Frischling
Keith A. Orso
Yite John Lu
David Gindler
MFleming@irell.com
gfrischling@irell.com
korso@irell.com
yjlu@irell.com
dgindler@irell.com
Genentech/RituxanIPR@irell.com

PAUL, WEISS, RIFKIND,
WHARTON & GARRISON LLP
J. Steven Baughman
Megan Raymond
sbaughman@paulweiss.com
mraymond@paulweiss.com
Grp-Biogen-821IPR@paulweiss.com

Date: July 5, 2018

/Michelle S. Rhyu/
Michelle S. Rhyu
Reg. No. 41,268
Counsel for Petitioner

Cooley LLP
Attn: Patent Docketing
1299 Pennsylvania Avenue NW
Suite 700
Washington D.C. 20004
Tele: 650-843-5505
Fax: 650-849-7400