UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner

v.

BIOGEN, INC.,
Patent Owner

Case IPR2017-01095
Patent 9,296,821

PATENT OWNER'S RESPONSE

LIST OF EXHIBITS

Patent Owner's Exhibit No.	Description
2001	S. Al-Ismail et al., *Combination Chemotherapy Including Epirubicin for the Management of Non-Hodgkin's Lymphoma*, European Journal of Cancer & Clinical Oncology, Vol. 23, No. 9 (May 11, 1987)
2002	P. McLaughlin et al., *Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program*, Journal of Clinical Oncology, Vol. 16, No. 8 (Apr. 29, 1998)
2003	U.S. Patent Application No. 11/840,956
2004	U.S. Patent No. 8,329,172
2005	U.S. Patent Application No. 10/196,732
2006	Patent Owner's Amendment and Reply under 37 CFR 1.111 for Application No. 11/840,956, dated Aug. 25, 2010
2007	Patent Owner's Amendment and Reply under 37 CFR 1.111 for Application No. 11/840,956, dated June 6, 2011
2008	Patent Owner's Reply and Amendment for Application No. 09/372,202, dated Sep. 14, 2001
2009	Carlson, Robert, *Rituximab plus CHOP: a new approach for non- Hodgkin's lymphoma?*, Inpharma No. 1116 (Dec. 6, 1997)
2010	Non-Institution Decision, *Boehringer Ingelheim International GmbH v. Biogen Idec, Inc.*, IPR2015-00418, Paper 14 (July 13, 2015)
2011	Declaration of Sharon Song
2012	Declaration of David Gindler
2013	Armando López-Guillermo et al., *The Clinical Significance of Molecular Response in Indolent Follicular Lymphomas*, Blood, Vol. 91, No. 8 (Apr. 15, 1998)
2014	Luigi Rigacci et al., *The Role of Anthracyclines in Combination Chemotherapy for the Treatment of Follicular Lymphoma: Retrospective Study of the Intergruppo Italiano Linfomi on 761 Cases*, Leukemia & Lymphoma, Vol. 44, No. 11 (Nov. 3, 2003)

2015	Rituxan® (Rituximab) Prescribing Information dated April 2016
2016	Declaration of Megan Raymond
2017	Richard I. Fisher, M.D., et al., *Comparison of a Standard Regimen (CHOP) With Three Intensive Chemotherapy Regimens for Advanced Non-Hodgkin's Lymphoma*, New England Journal of Medicine, Vol. 328, No. 14 (Apr. 8, 1993)
2018	P. McLaughlin et al., *CHOP-BLEO Plus α-Interferon (IFN) in Stage IV Low Grade Lymphoma (LGL)*, American Society of Clinical Oncology, Vol. 11 (Mar. 1992) (Abstract 1109)
2019	Richard V. Smalley et al., *Interferon Alfa Combined with Cytotoxic Chemotherapy for Patients with Non-Hodgkin's Lymphoma*, New England Journal of Medicine, Vol. 327, No. 19 (Nov. 5, 1992)
2020	Han T. et al., *Chlorambucil vs. Combined Chlorambucil-Corticosteroid Therapy in Chronic Lymphocytic Leukemia*, Cancer, Vol. 31, No. 3 (Mar. 1973)
2021	John G. Gribben et al., *Detection of Residual Lymphoma Cells by Polymerase Chain Reaction in Peripheral Blood Is Significantly Less Predictive for Relapse Than Detection in Bone Marrow*, Blood, Vol. 83, No. 12 (June 15, 1994)
2022	Bruce Raphael et al., *Comparison of Chlorambucil and Prednisone Versus Cyclophosphamide, Vincristine, and Prednisone as Initial Treatment for Chronic Lymphocytic Leukemia: Long-Term Follow-Up of an Eastern Cooperative Oncology Group Randomized Clinical Trial*, Journal of Clinical Oncology, Vol. 9, No. 5 (May 1991)
2023	Ediz Z. Ezdinli & Leon Stutzman, *Chlorambucil Therapy for Lymphomas and Chronic Lymphocytic Leukemia*, Journal of American Medical Association, Vol. 191, No. 6 (Feb. 8, 1965)
2024	Anton Hagenbeek et al., *Maintenance of Remission With Human Recombinant Interferon Alfa-2a in Patients With Stages III and IV Low-Grade Malignant Non-Hodgkin's Lymphoma*, Journal of Clinical Oncology, Vol. 16, No. 1 (Jan. 1, 1998)

2025	B. A. Peterson et al., *Nodular Mixed Lymphoma (NML): A Composite Trial of Cyclophosphamide (CTX) and Cyclophosphamide, Adriamycin, Vincristine, Prednisone and Bleomycin (CAVPB)*, Blood, Vol. 66, No. 5 (Nov. 1985)
2026	Peter McLaughlin et al., *Stage III Follicular Lymphoma: Durable Remissions with a Combined Chemotherapy-Radiotherapy* Regimen, Journal of Clinical Oncology, Vol. 5, No. 6 (June 1987)
2027	Deposition Transcript of Petitioner's Expert Dr. Izidore Lossos dated Jan. 25, 2018
2028	Stanley J. Korsmeyer, *Bcl-2 Initiates a New Category of Oncogenes: Regulators of Cell Death*, Blood, Vol. 80, No. 4 (Aug. 15, 1992)
2029	Declaration of Peter McLaughlin, M.D

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES

OTHER AUTHORITIES

I. INTRODUCTION

U.S. Patent No. 9,296,821's ("'821") breakthrough invention led to vastly improved treatment for countless low-grade/follicular non-Hodgkin's lymphoma ("LG/F-NHL") patients. Petitioner's attacks on that invention rest on assumptions and logical leaps its Petition ("Pet.," Pap. 2) failed to support. Patent Owner Biogen, Inc. ("PO") now addresses the Petition's numerous errors and omissions, supported by Dr. McLaughlin's expert testimony (EX2029), and free of §42.108(c)'s institution-only constraints.[1] Claims 1-3, 5, and 6 ("Challenged Claims") are directed to methods of administering rituximab, an immunotherapeutic, during CVP chemotherapy—a more effective treatment regime for LG/F-NHL patients that, *inter alia*, provides a "beneficial synergistic effect" greater than the additive effects of its separate components, and lessens the likelihood and frequency of relapse observed with chemotherapy-only regimens. EX1001, 3:42-47; 2:7-8. Because Petitioner's evidence fails to establish obviousness or anticipation for any instituted ground, the patentability of every Challenged Claim must be confirmed.

[1] Unless noted, all emphasis is added and all section references are to 35 U.S.C. or 37 C.F.R., as context indicates.

First, Petitioner fails to demonstrate that its key "prior art" and background documents are actually printed publications—a failure fatal to every instituted ground.

The bulk of Petitioner's instituted obviousness challenges[2] rest on an argument that persons of ordinary skill in the art[3] ("POSITA") would take one reference—a short abstract by Czuczman (EX1011) reporting a remarkably-successful treatment combining rituximab with a particular collection of chemotherapy drugs known as "CHOP"—and inexplicably *change* that successful combination. But as detailed below, without the benefit of the '821's disclosure, POSITA would have had no reason to alter Czuczman as Petitioner argued. Petitioner asserted it would have been obvious to eliminate doxorubicin, one of the CHOP drugs. But Petitioner failed to show why POSITA would have done so *in 1999*, when doxorubicin was understood to be *the only CHOP component* known to produce a beneficial result when combined with rituximab,

---

[2] Should Petitioner or another party invoke non-instituted grounds or "evidence," or improperly make new arguments in Reply, PO reserves the right to respond.

[3] Because it does not impact the outcome, it is unnecessary to address Petitioner's POSITA definition. *Genband US LLC v. Metaswitch Networks Ltd.*, IPR2015-01457, Pap. 38 (Final Written Decision ("FWD")), 19 (Dec. 15, 2016).

and when immunotherapy combinations were known to be extremely unpredictable. Further, Petitioner failed to prove this chemotherapy combination *without* doxorubicin (called "CVP") and with rituximab would have been expected to achieve clinical results anything like the surprising efficacy of rituximab+CHOP ("R-CHOP")—particularly given that CVP was deemed less aggressive and less effective than CHOP, and that with R-CHOP Czuczman reported a *100% response rate* and remarkable clearance of a condition ("*bcl-2* positivity") linked to relapse.

The many flaws in Petitioner's attempt to cobble together the '821 invention from the prior art are further highlighted by the Board's proper exclusion of "IDEC's 10-K/A" (EX1006). Petitioner presented Exhibit 1006 as the sole bridge connecting Czuczman to Foon and Dana for *all* obviousness arguments against Claims 1-3: Exhibit 1006 was the *only* proffered reason to substitute other chemotherapy drugs into Czuczman's successful R-CHOP combination. Without that bridge, Petitioner's obviousness arguments fall apart.

For these and other reasons below (including Petitioner's erroneous assertions about the claim 5-6 priority), the patentability of each Challenged Claim should be confirmed.

II. BACKGROUND

Non-Hodgkin's lymphoma ("NHL") is a "diverse group of diseases ranging from the very aggressive and rapidly fatal to the more indolent." EX2001, 004;

EX2029, ¶27. Approximately 80% are B-cell malignancies (EX1001, 5:40-41), classified into sub-types including, *e.g.*, low-grade tumors and rapidly-growing and aggressive intermediate- or high-grade malignancies. EX1008, 024; EX2029, ¶27. Low-grade ("LG") lymphoma, though slow growing, is nevertheless deadly. EX1001, 4:49-52; EX2029, ¶27. Follicular lymphoma ("FL") is the most common low-grade NHL, characterized by slow growth and high initial response rates, but typically followed by relapse and progressive disease. EX1020, 002; EX2029, ¶28. "The terminal course is often characterized by transformation to a more malignant histology, by extranodal progression of disease, and by drug resistance." EX1009, 002; EX2029, ¶28.

A. Multiple Chemotherapeutic Options for Treating LG/F-NHL Existed But None Had a Particular Advantage With Respect to Overall Survival

Before the '821, there were numerous single-agent and combination chemotherapeutic options for LG/F-NHL. *E.g.*, EX1008, 029-30; EX2029, ¶34. For example, Petitioner's purported Foon and Dana references identified an assortment of chemotherapy alternatives, including at least five different single agents (chlorambucil and high-dosed pulsed chlorambucil, cyclophosphamide, fludarabine, pentostatin, cladrabine) and at least eight combination chemotherapies (COPP (and C-MOPP), CVP, CHOP, ProMACE/MOPP, CHOP-bleomycin,

CNOP, OAP, and CVP+BCNU) used to treat LG/F-NHL.[4] EX1008, 029-30; EX1009, 005-6 & Table 5; EX2029, ¶35. *See also* EX2027 46:21-48:23; 49:24-50:16; 44:9-18. But as another Petitioner exhibit explains, despite high overall and complete clinical responses, the median duration of survival of 6 to 10 years remained unaltered. EX1025, 003; EX2029, ¶36. Investigators believed this was, in part, because they targeted *rapidly dividing* cells, whereas LG/F-NHL cells divide at relatively *lower rates*. EX1025, 003; EX2029, ¶37. Patients invariably relapsed (EX2013, 00001) and Dana (EX1009, 003) reported remission averaged only about two years. Petitioner's EX1005 noted subsequent remissions with further treatment, but at a lower rate and ever-shorter duration. *Id.* 003. As Petitioner observed, "[m]ost patients eventually die from the disease or its complications." Pet. 7.

One posited explanation for the failure of chemotherapy to extend LG/F-NHL survival was the persistence of *bcl-2*-positive cells, even after complete response to chemotherapy. EX1025, 004; EX2009, 001; EX2013, 00001; EX1002 (Petitioner's Dr. Lossos), ¶104 (Czuczman reported "standard chemotherapy regimens alone have been unable to clear BCL-2 translocation positive cells")

[4] Dr. Lossos identified additional LG-F/NHL chemotherapy treatments as well. EX2027, 46:21-48:23; 49:24-50:16.

EX2029, ¶¶29-33. For example, most FLs contain a chromosomal rearrangement leading to overexpression of *bcl-2*, which, in turn, was believed to inhibit cell death, giving *bcl-2*-positive cancer cells a survival advantage. EX1025, 004; EX1020, 002-3; EX2021, 00001; EX2013, 00001 EX2029, ¶¶31-32. Researchers thought *bcl-2* also played an important role in LG/F-NHL disease development. EX1025, 004; EX1020, 002-3; EX2009, 001; EX2029, ¶32. This belief was supported by the observation that the presence of *bcl-2*-positive cells in the marrow after treatment had value in predicting relapse, and molecular expression of *bcl-2* was considered a surrogate marker for residual/recurrent LG/F-NHL. EX2021, 00001; EX2013, 00001; EX1025, 004; EX2029, ¶33. Clinicians believed that, for treating LG/F-NHL, it was important not only to achieve complete *clinical* remission, *i.e.*, "complete responses," but also complete *molecular* remission by eradicating *bcl-2* positive cells. EX2009, 001; EX2029, ¶33. Relapse was believed to arise from residual lymphoma cells below detectable limits. (EX2013, 00001; EX2021, 001) EX1025, 004; EX2009, 001; EX2029, ¶38; EX1002, ¶104.

Although no chemotherapeutic option improved overall survival, a combination regimen consisting of ***C***yclophosphamide, Doxorubicin ("***H***"[5]),

[5] Doxorubicin is also known as "***h***ydroxydaunorubicin," and "Adriamycin" ("***A***"). EX1002, ¶39; EX2029, ¶39.

Vincristine ("***O***"[6]), and ***P***rednisone ("***CHOP***") was an "effective first-line therapy for low-grade or follicular NHL." EX1021, 004; EX2029, ¶39. CHOP treatment improved overall outcomes by improving clinical response rates. EX2014, 00006; EX2029, ¶39. Other chemotherapeutic options, such as ***CVP*** (***C***yclophosphamide, ***V***incristine, and ***P***rednisone), produced less-favorable results, including lower remission rates and shorter duration of response, as Petitioner's expert concedes. EX2027, 40:2-19; EX2029, ¶40.EX1042, 001. Similarly, Dana reported CHOP therapy combinations produced better response rates than single-agent therapies. EX1009, 003; EX2014, 00008; EX2029, ¶40.

B. Use of Immunotherapy in Cancer Treatment Was New, and Immunotherapy Combinations Were Unpredictable

At the time of the '821, "immunotherapy" referred to biologic agents affecting the immune system. E.g., EX1008, 033-34; EX2029, ¶41. When combined with chemotherapy, the combination is a "chemoimmunotherapy." EX2029, ¶40.

Early attempts to treat NHL with monoclonal antibodies, before rituximab, were largely unsuccessful. EX1064, 004; EX2029, ¶42. Rituximab binds CD20 (a

---

[6] Vincristine ("***V***")) is also is known by the brand "***O***ncovin." Pet., 8 n.1. Thus, C***V***P is sometimes called "C***O***P." EX2029, ¶39 .

protein on B cells' surface), leading to depletion of those B cells by the immune system. EX1001, 1:59-61, 15:24-26.[7] The FDA initially approved rituximab in 1997 as monotherapy to treat relapsed or refractory LG/F-NHL, which was a significant breakthrough because of its long-term efficacy—but "patients [were] often subject to disease relapse." EX1064, 005; EX1001, 1:58-61, 1:67-2:2.

Because treatment with monoclonal antibodies like rituximab was believed "extremely effective *in a minimal residual disease setting*" (EX1020, 004), an aggressive chemotherapeutic regimen, like CHOP, was favored to minimize tumor burden for immunotherapy treatment. EX2029, ¶43. Beneficial clinical outcomes with immunotherapy combinations were not predictable. *See infra*, §V.C.1; EX2029, ¶44. For example, 80% of Foon's disclosed immunotherapy combinations were ineffective with respect to objective response rates. EX1008, 033; EX2027, 37:21-38:18; EX2029, ¶44.

C. Petitioner's "Czuczman" Document Reported Remarkable Results With R-CHOP

Seeking "new therapeutic strategies with improved antitumor activity and acceptable toxicity," Dr. Czuczman hypothesized that R-CHOP would improve outcomes (EX1028, 006), stating "[t]he rationale for combination of IDEC-C2B8

[7] Rituximab is also known by its name in development, "C2B8." *Id.*, 3:3-5.

[rituximab] with CHOP includes non-cross-resistant mechanism of action, individual efficacy, nonoverlapping toxicities, and ***known synergy with doxorubicin***" (the "H" in CHOP). EX1041, 003. This combination was first tested in patients with LG/F-NHL because no known treatment was curative. EX1028, 006; EX1041, 003; EX2029, ¶45.

As Petitioners recognize (Pet. 46), the "Czuczman" investigators reported extraordinary results:

- "Overall response rate for the 14 [patients] completing all scheduled therapy to date is ***100%***." EX1011, 003; EX1002, ¶57.
- No "unexpected toxicities" were observed. EX1011, 003.
- And, remarkably, this 100% response rate was maintained through study completion even with 24 more patients, bringing total responses to 38 of 38 patients receiving treatment. EX1020, 003 (median time to progression not yet reached even after median observation time greater than 29 months).

EX2029, ¶46. Czuczman's reported 100% response rate was beyond "impressive," even according to Petitioner's expert's standards. EX1002, ¶60 (describing overall response rate of 96% as "impressive"). Notably, this combination also led to complete *molecular* remissions:

- Of the four patients found to be *bcl-2* positive, all tested *bcl-2* negative after completing treatment. EX1011, 003; *see also* EX1020, 009; EX2029, ¶47; EX1002, ¶104.[8]

D. Petitioner's Instituted References Fail to Meet Its Burden

Petitioner not only failed to demonstrate its various purportedly key prior art references (*e.g.*, EX1005, EX1008, EX1009, EX1011) are actually the prior art printed publications Petitioner claims (*e.g.*, §IV, *infra*)—it also misrepresented their disclosures and failed to match them to the Challenged Claims' requirements.

For example, none of Petitioner's Czuczman, Foon, or Dana references instituted for claims 1-3 (EX1011, EX1008, EX1009), individually or in combination, discloses or suggests a combined therapy R-CVP for LG/F-NHL, as those claims require. EX2029, ¶¶49, 52. Petitioner concedes Czuczman discloses R-CHOP was safe and efficacious. EX1002, ¶108; EX2029, ¶50. But while Czuczman reported remarkable efficacy for LG/F-NHL and "encouraging" toxicity with R-CHOP, *e.g.*, EX1011, 003; EX1041, 003; EX2029, ¶50, it never suggested substituting *CVP* or any other chemotherapy for CHOP (*e.g.*, EX1002, ¶¶57, 108

[8] In later work with additional patients, seven of eight tested *bcl-2* negative after treatment. EX1020, 009.

(Petitioner's Lossos relying on EX1011 *to disclose R-CHOP*)), and never disclosed the kind of "beneficial synergistic effect" required by claim 1.[9] EX2029, ¶51.

Petitioner also falsely portrays Foon and Dana as teaching POSITA had a binary choice between CHOP and CVP for rituximab combination in treating LG/F-NHL. *E.g.*, Pet. 7-10. But Foon and Dana collectively disclose at least 13 chemotherapy options POSITA could have considered for combination with rituximab if the Petition had shown a reason to do so (it didn't). EX2029, ¶52. And Petitioner's Dr. Lossos concedes physicians affirmatively considered and used various alternatives beyond "CVP versus CHOP" (including, *e.g.*, "single agent regimens of cyclophosphamide or chlorambucil") as common chemotherapy regimens. *E.g.*, EX1002, ¶44; EX2027, 40:4-11, 43:11-18 (acknowledging chlorambucil considered by some physicians as standard, less toxic alternative to

[9] Czuczman expressly confirmed R-CHOP had only "additive therapeutic benefit." Ex. 1020, 002. The single abbreviated mention in Czuczman's abstract (EX1011, 003) of "synergy with chemotherapeutic agents" as "[t]he *rationale for combination* of [rituximab] with CHOP," simply pointed to earlier *in vitro* "sensitiz[ation]" experiments as a reason to experiment with R and CHOP—*it did not describe any results of Czuczman's experiments*. *See* §VI.B, *infra*; EX2029, ¶51.

CHOP), 43:11-18; 48:10-23; 49:24-50:4. Moreover, as detailed *infra* §V.C.1, Foon confirms what POSITA knew: immunotherapy combinations were unpredictable and did not necessarily lead to additive or neutral (much less synergistic) results. And neither Foon nor Dana *ever* suggests altering Czuczman's R-CHOP combination, let alone *with CVP*. EX2029, ¶53. Indeed, as Dr. Lossos now concedes—contradicting his original testimony that "CVP was…less toxic but equally effective as CHOP for low-grade NHL" (EX1002, ¶108)—CHOP was *more* effective than CVP in both duration of response and remission rates, as shown by EX1047, which he cited. *See also* EX2029, ¶108; EX2027, 38:1-40:19. And Dr. Lossos admitted he may have omitted more studies from his report showing that CHOP is more effective than CVP. EX2027, 42:14-43:3.

The Petition—both in what it cited[10] and what it ignored—failed to meet Petitioner's burden on any instituted ground.

---

[10] Petitioner pointed briefly to EX1065 and EX1066, related to an alleged "E1496 trial," but tied it to no relevant issue, identified no study results, and improperly incorporated by reference many paragraphs of the corresponding expert declaration (EX1003). Pet. 16-17. In any case, these were not identified in Petitioner's obviousness combination. Further, Petitioner admitted the E1496 study related to maintenance therapy, not immunotherapy during chemotherapy, which is the issue

III. CLAIM CONSTRUCTION

In IPRs, "[a] claim in an unexpired patent…shall be given its broadest reasonable construction in light of the specification of the patent in which it appears." §42.100(b). Petitioner proposes construing "beneficial synergistic effect," but otherwise relies on plain and ordinary meaning. Pet. 30. Consistent with the Board's determination at institution (Pap. 12 ("Dec."), 7), it should reject Petitioner's construction, which reads out "synergistic." The Board should also adopt PO's "C2B8" construction, with which Petitioner agrees.

A. "Beneficial Synergistic Effect" (Claim 1)

Claim 1 recites administering rituximab during a CVP regimen "wherein the method provides a beneficial synergistic effect in the patient." As the Board correctly recognized at institution (Dec. 7), the intrinsic evidence makes clear a "beneficial *synergistic* effect" for a two-therapy combination is not just *any* beneficial effect, but an effect better than the additive effects of the therapies administered alone. Accordingly, the Board should construe "beneficial

---

here. *See* Pet. 16 ("to test the effectiveness of Rituximab *maintenance therapy* following CVP therapy"). Finally, Petitioner did not meet its burden to establish these exhibits qualify as prior art and did not establish how a POSITA would have been able to obtain the protocol (EX1065). *See* §IV, *infra*.

synergistic effect" to mean "an effect better than the additive effects of rituximab and CVP administered alone" (as PO's Preliminary Response proposed (Pap. 10, 9-14)) or "a clinical outcome resulting from combination therapy that reflects a greater beneficial effect than the additive effects of the uncombined therapies when administered alone" (as the Board correctly found (Dec. 7)). Either of these comparable constructions is properly used here. Petitioner's proposal, which improperly reads out "synergistic," must be rejected.

1. The Intrinsic Evidence Supports PO's Construction

The specification explains what "synergistic" means, disclosing "it has been found that treatment with anti-CD20 antibody provides a beneficial synergistic effect when administered in combination with cytokines, radiotherapy, myeloablative therapy, or chemotherapy." EX1001, 2:24-28. In discussing a cytokine embodiment, the patent confirms a "*synergistic*" therapeutic combination produces an effect "*better than the additive effects* of either therapy administered alone." EX1001, 3:44-47.

This construction was also confirmed during the '821's parent's prosecution, where applicant similarly equated more-than-additive results with "synergistic." In observing data from a study after the priority date, applicant wrote: "The complete responses (CRs) and extended median TTP [Time To disease Progression] achieved with the presently claimed combination were more than additive, *i.e.* they

were synergistic results." EX2006, 014-015; EX2007, 032-033 (noting results "were more than additive, *i.e.*, they were synergistic results"). *Abbott Labs. v. Novopharm Ltd.*, 323 F.3d 1324, 1327–28, 1330 (Fed. Cir. 2003) (term "explicitly defined" by specification's use of "*i.e.*").

Applicant cited this same data during '821's prosecution, stating "the evidence of-record confirms that the method provides a beneficial synergistic effect in the patient as recited in claim 1." EX1069, 137; *id.* 121 ("These data point to the beneficial synergistic effect…and would have been unexpected"). And during prosecution of the '821's great-grandparent, applicant similarly argued "[e]vidence of a greater than expected results may be shown by demonstrating an effect which is *greater than the sum of each of the effects taken separately (i.e., demonstrating 'synergism')*." EX2008, 011 (citing *Merck & Co. Inc. v. Biocraft Labs. Inc.*, 874 F.2d 804 (Fed. Cir. 1989)); *Abbott*, 323 F.3d at 1327–28, 1330.

Thus, both the specification and prosecution history support PO's construction.

2. Petitioner's Construction Ignores "Synergistic"

Petitioner's expert admitted *Petitioner's* construction is *inconsistent with the '821 specification*, and stated he would apply the Board's interpretation going forward. EX2027, 32:1-20; *see also Trs. of Columbia Univ. v. Symantec Corp.*, 811 F.3d 1359, 1362–64 (Fed. Cir. 2016) (construction analysis must start with

claims and specification; improper to start analysis with supposed "plain and ordinary meaning" before consulting specification). Petitioner's proposal—"an improvement in clinical outcome" (Pet. 31)—ignores "synergistic" in "beneficial ***synergistic*** effect." *See Funai Elec. Co. v. Daewoo Elecs. Corp.*, 616 F.3d 1357, 1372 (Fed. Cir. 2010) ("We must give meaning to *all the words* in [the] claims"); *Ex Parte Behzad*, Appeal 2011-007124, 2014 WL 1311619, at *2 (P.T.A.B. Mar. 28, 2014).

Petitioner tries to justify its construction by citing the summary and background of the invention sections, generally stating "it would be 'beneficial if more effective treatment regimens [than rituximab monotherapy] could be developed.'" Pet. 30-31. But both excerpts are consistent with *PO's* construction. A method of administering rituximab during CVP chemotherapy yielding "an effect better than the additive effects of rituximab and CVP administered alone" is, by definition, a more effective treatment regimen than rituximab monotherapy.

According to Petitioner, "[d]uring prosecution, Applicant argued that data referenced in the 2006 label (EX1060) and the Marcus publication (EX1005) showed that patients who received rituximab during CVP chemotherapy . . . 'demonstrat[ed] a beneficial synergistic effect in the patient[s].'" Pet. 31 (quoting EX1069 ('821 file history), 120). But in attempting to argue any "improvement"

constitutes "a beneficial synergistic effect" (*id*.), Petitioner omits the data applicant summarized *on the next page of Petitioner's cited exhibit:*

Treatment Regimen	Median Time to Progression (TTP) (months)	Complete Response (CR) (% of patients)
Rituximab (R)	9 months*	6%**
Cyclophosphamide, Vincristine, Prednisolone (CVP)	15 months#	10%#
R-CVP	32 months#	41%#

* Marcus et al. top column 1 on page 1418
** Present application, page 20, line 3
# Marcus et al., abstract

EX1069, 121. Petitioner never contended, much less showed, this data is inconsistent with an effect for R-CVP *better than the additive effects* of rituximab and CVP administered alone, as PO's construction requires.

B. "C2B8"

The specification and prosecution history disclose "C2B8" is rituximab. EX1001, 3:3-5; EX2008, 00005. Petitioner agrees. *See, e.g.*, Pet. 41, 14 n.4; EX2027, 91:8-9 (Lossos). Thus, "C2B8" should be construed as "rituximab."

IV. THE PETITION FAILED TO ESTABLISH THAT FOON, CZUCZMAN, DANA, MARCUS, AND OTHER CITED REFERENCES ARE PRIOR ART PRINTED PUBLICATIONS

Whether a document is a §102 "printed publication" "involves a case-by-case inquiry into the facts and circumstances surrounding the reference's disclosure to members of the public." *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004). The key inquiry is "sufficient[] accessib[ility] to the public

interested in the art" before the critical date. *In re Cronyn*, 890 F.2d 1158, 1160 (Fed. Cir. 1989); *In re Wyer*, 655 F.2d 221, 226 (C.C.P.A. 1981). "A given reference is 'publicly accessible' upon a satisfactory showing [it] has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *Suffolk Techs., LLC v. AOL Inc.*, 752 F.3d 1358, 1364 (Fed. Cir. 2014) (quoting *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008)). It is Petitioner's burden to show printed publication status by a preponderance of the evidence. *Smart Microwave Sensors GmbH v. Wavetronix LLC*, IPR2016-00488, Pap. 57 (FWD), 25 (July 17, 2017).

The Petition did not even *attempt* to show Foon, Czuczman, Dana, or Marcus are actually prior art printed publications. Petitioner merely asserted this is so. Pet. 31-35. The Petition thus failed to establish its references are prior art printed publications and authentic. *See, e.g., ABS Glob. Inc. v. Inguran, LLC*, IPR2016-00927, Pap. 33 (FWD), 19 (Oct. 2, 2017) (article was not publicly accessible where petitioner "has not presented evidence to establish that as fact"); *TRW Auto. U.S. LLC v. Magna Elecs., Inc.*, IPR2014-01347, Pap. 25 (FWD), 8-9 (Jan. 6, 2016) ("copyright notice is … not probative that the article was ever published by IEEE or anyone else."). Tellingly, the Petition and its supporting

evidence said nothing about where the pages Petitioner attaches as exhibits were found or generated.

Petitioner baldly asserted Foon was published and publicly available, but with no explanation or proof of either. Pet. 34. Similarly, for Marcus, Czuczman, and Dana Petitioner merely asserted these exhibits came from journals and asserted a publication date for each. Pet. 32-35. But Petitioner provided no *evidence* establishing these came from those journals, where the journals were found, or that the journals were regularly published; nor did the Petition even *assert* this was so. And the Petition never explained how Petitioner came up with the asserted publication dates: to the extent Petitioner relied on a copyright or other date on the document, this is hearsay, and Petitioner provided no showing any exception might apply. *See Smart Microwave Sensors*, IPR2016-00488, Pap. 57, 25 ("copyright notice date or other alleged publication data on the document is hearsay, to which no exception applies"; "even if admissible, such dates alone are accorded little weight to prove public accessibility"); *Standard Innovation Corp. v. LELO, Inc.*, IPR2014-00148, Pap. 41 (FWD), 22 (Apr. 23, 2015). And in any case, even if such a date were not hearsay, it would not have established public availability. *ABS Glob.*, IPR2016-00927, Pap. 33, 17–18; *Smart Microwave Sensors*, IPR2016-00488, Pap. 57 (FWD), 31 (Copyright Office records regarding textbook

published by John Wiley & Sons and bearing copyright date, without more, "insufficient").[11]

Petitioner has also not shown its various background references (*e.g.*, 1013-1022, 1024-1025, 1027-1028, 1030-1033, 1036, 1038-1039, 1041, 1043-1051, 1053-1061, 1064-1066, 1068, 1070-1071, 1074-1075, 1078-1081) are actually prior art. For example, Petitioner cited what it calls a Rituxan® label (EX1019), without providing information to establish what it is, or if and when it was published. *See, e.g.*, *Carefusion Corp. v. Baxter Int'l, Inc.*, IPR2016-01463, Pap. 38 (FWD), 31-35 (Jan. 2, 2018) (manual containing directions not shown publicly accessible without proof of sales containing manual); *Aceto Agric. Chem. Corp. v. Gowan Co.*, IPR2016-00076, Pap. 51 (FWD), 22 (Apr. 28, 2017) (date on reference does not prove public availability); *Oxford Nanopore Techs., Ltd. v.*

[11] Dr. Lossos asserts "Williams Hematology," in which Foon is allegedly a chapter, is a renowned treatise. EX1002, ¶38. But, *inter alia*, his conclusory assertion provides no information about its public availability *by 1999*. Moreover, Petitioner never cited this paragraph in the Petition, and thus waived any such reliance. *E.g.*, *Spectrum Brands, Inc. v. Assa Abloy AB*, IPR2015-01562, Pap. 35 (FWD), 33 n.8 (Jan. 12, 2017) (declining to consider reasons discussed in expert declaration but not in petition).

Univ. of Wash., IPR2014-00513, Pap. 51 (FWD), 34-35 (Feb. 26, 2016) (abstract not printed publication); *see also TRW Auto.*, IPR2014-01347, Pap. 25 (FWD), 7 (online article allegedly from IEEE not authenticated and therefore not printed publication); *Liberty Mut. Ins. Co. v. Progressive Cas. Ins. Co.*, CBM2013-00009, Pap. 68 (FWD), 18 (Feb. 11, 2014) (although "10-K is an official record, that does not mean it is a printed publication"). Thus, these references should not be considered for any purpose.[12]

V. CLAIMS 1-3 ARE NOT OBVIOUS BASED ON CZUCZMAN, FOON, DANA, AND THE '137 PATENT

The Board instituted review of claims 1-3 on obviousness based on Czuczman, Foon and Dana, and on claim 3 based on Czuczman, Foon, Dana, and the '137 Patent. Dec. 34. But Petitioner argued both combinations required reliance on EX1006 ("IDEC's 10-K/A"), which the Board properly determined had

---

[12] Petitioner's Exhibits 2013-2015, 2017-2026, 2028 are authentic, and were found where, if authentic, they would likely be. *See* EX2016. Further, EXS 2001-02, 2013, 2017-2019, 2021, 2024, 2026, 2028 were publicly available prior to August 1999 and a POSITA could have easily found them. EX2029, ¶¶127. Similarly, at least EXS2001-02, 2009, 2017- 2026, 2028 are ancient documents under FRE 803(16), and the hearsay exception therefore applies to the content.

not been shown to be prior art. Further, even apart from this unfilled gap in proof, these combinations are unsupported.

A. The Petition Lacks Any Explanation of a Motivation to Combine Without "IDEC's 10-K/A"

As a crucial initial step for obviousness, Petitioner was required to show a motivation to combine. But it failed to do so in multiple respects, including by relying entirely on a document the Board rejected: Petitioner's obviousness arguments and evidence for claims 1-3 all *expressly required and depended upon* Petitioner's Exhibit 1006, which the Board excluded from institution. *E.g.*, Pet. 45; Ex 1002, ¶¶102-12; Dec. 19-21.

Czuczman's teachings and disclosed treatment regimen were limited to ***CHOP***. *See, e.g.*, EX1011; EX1002, ¶¶57, 108 (relying on EX1011 for disclosure of R+ *CHOP*). To try to bridge from Czuczman's successful R-CHOP combination to an alteration that *replaced* CHOP, *Petitioner and its expert relied solely and entirely on Exhibit 1006* for a connection to Foon and Dana. Specifically, Petitioner asserted EX1006 alone provided a suggestion of "combining rituximab with *other* standard chemotherapy regimens for low-grade lymphoma," and was the supposed reason for POSITA to look to Foon and Dana for standard chemotherapies. Pet. 48; EX1002, ¶¶105, 64-65 ("A POSA would have been motivated *by the IDEC SEC 10-K/A disclosures* to combine rituximab

maintenance therapy with standard chemotherapy regimens."); Pet. 45, Ex 1002, 102-12.

But the Board correctly *excluded* EX1006. Dec. 19-21. And although the Board stated it "analyze[d] Petitioner's remaining grounds without considering the IDEC 10-K/A as a prior art printed publication," *id.* at 21, Petitioner's evidence included no alternative support for any motivation to combine, and thus failed to address the hole in Petitioner's arguments and evidence by the removal of EX1006. The remaining combination lacks *any motivation* to try chemotherapy other than R-CHOP.

Respectfully, Petitioner is only permitted to rely on—and PO can only be expected to respond to—the arguments Petitioner actually made in its Petition. *See, e.g.*, *Intelligent Bio–Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–68 (Fed. Cir. 2016) (affirming rejection of reply brief because Petitioner relied on new rationale); *Colas Sols. Inc. v. Blacklidge Emulsions, Inc.*, IPR2016-01031, Pap. 38 (FWD), 26 (Nov. 2, 2017) (it is of the "utmost importance that petitioners … [in] initial petition identify 'with particularity' the 'evidence that supports the grounds for the challenge to each claim,'" quoting *Intelligent Bio–Sys.*, 821 F.3d at 1369); *Dell Inc. v. Acceleron, LLC*, IPR2013-00440, Pap. 49, 13 (Aug. 22, 2016) (declining to analyze inherency where petition argued express disclosure). With EX1006's exclusion, Petitioner

failed to meet its burden for claims 1-3. *See In re Nuvasive, Inc.*, 842 F.3d 1376, 1381–85 (Fed. Cir. 2016) (vacating obviousness finding failing to articulate why POSITA "would have been motivated to modify" art).

B. POSITA Would Not Have Been Motivated to Replace CHOP With CVP Given Czuczman's Teachings

1. Czuczman Discloses Only R-CHOP

As discussed above, Petitioner's primary reference, Czuczman, is an abstract disclosing the combined use of rituximab ("C2B8") and CHOP to treat LG/F-NHL. EX1011, 003. Indeed, from Czuczman's title, "IDEC-C2B8 *and CHOP* Chemoimmunotherapy of Low Grade Lymphoma," POSITA would understand Czuczman focuses exclusively on combining rituximab ***with CHOP***—not CVP, as the Challenged Claims require, or with chemotherapy generally. EX2029, ¶54. Indeed, Petitioner does not even suggest Czuczman says anything about a combination with CVP.

Czuczman experimented with treating low-grade lymphoma with standard-dose CHOP and rituximab and reported clinical outcomes—based on response rates—as showing "anti-tumor activity of CHOP and IDEC-C2B8 is superior to CHOP therapy alone." EX1011, 003. They reported and suggested nothing concerning other chemotherapies (much less CVP). EX2029, ¶55. POSITA reading this abstract, as well as Czuczman's further elaborations on these results,

would not be motivated to discard CHOP in favor of another chemotherapy agent like CVP. EX2029, ¶55.

2. POSITA Would Not Have Been Motivated to Replace CHOP With CVP Because of the Remarkable Results from Czuczman's Rituximab+CHOP Treatment

POSITA reading Czuczman would not have been motivated to replace CHOP with CVP in Czuczman's R-CHOP regimen, because R-CHOP yielded a truly remarkable (1) 100% response rate and (2) conversion to *bcl-2* negativity (molecular complete remission) in initially *bcl-2* positive patients. EX1011, 003; EX2029, ¶56. In particular, at the time of '821, POSITA starting with Czuczman would not have turned from this powerfully-successful CHOP combination to an unknown combination with CVP for several reasons.

First, EX1011 reported efficacy based on response rates and *bcl-2* clearance, and POSITA would thus have considered these clinical endpoints in deciding whether R-CVP would be "equally effective" as R-CHOP, not *ignored* them as Petitioner does.[13] *Cf.* EX1002, ¶108. *See* EX2029, ¶57. Petitioner relies on "overall survival" alone as the relevant endpoint in concluding a POSITA

[13] Indeed, overall survival is *not mentioned* in EX1011, and thus cannot be the sole endpoint for efficacy comparisons (especially since Lossos argues they are "indistinguishable" on this endpoint (EX1002, ¶111)). EX2029, ¶57.

would substitute CVP for CHOP. EX1002, ¶¶38, 40-43, 109. But, a POSITA would not have ignored these Czuczman endpoints, which were understood to be worse for CVP as compared to CHOP. EX2029, ¶57. *Contrast* EX1002, ¶108; *with* EX2027, 40:11-19 (remission rates higher for CHOP).

Second, the inclusion of anthracyclines like doxorubicin (the "H" in "CHOP") *in particular* was understood to provide a benefit with rituximab, and POSITA would have feared losing this benefit (and thus Czuczman's 100% response rate) in moving to CVP and removing doxorubicin. EX1041, 003; EX1079, 008; EX2029, ¶¶58, 44-45. Indeed, this understanding was a known motivation for Czuczman's experimenting with R-CHOP (EX1041, 003; EX1021, 004; EX2009, 00001), and POSITA would not have been dissuaded from this view by Czuczman's 100% response rate. EX2029, ¶58.

Third, while no cure for LG/F-NHL existed, CHOP was known to be curative in certain NHLs (*e.g.*, EX1008, 030; EX1059, 003) and was thus favored for combining with rituximab to achieve durable responses. EX2029, ¶59.

Fourth, POSITA would not have anticipated that R-CVP would result in *bcl-2* conversion. EX2029, ¶¶60-63.

By the time of the '821, POSITA knew "approximately 80% of low-grade NHL" was associated with chromosomal translocation of a gene called "*bcl-2*." EX1020, 009; EX2029, ¶61. They further understood *bcl-2* overexpression may

lead to resistance to apoptosis (programmed cell death) and confer resistance to a variety of chemotherapeutic agents, including "certain alkylating agents, doxorubicin, glucocorticoids, and vincristine." EX1041, 002-003; EX2029, ¶61. POSITA also knew that residual *bcl-2* positive cells were associated with LG/F-NHL *relapse* (EX1041, 003; EX2029, ¶61; *cf.* EX1002, ¶104), and that patients' "*bcl-2* positive" state could be monitored by PCR. EX1020, 005; EX2029, ¶61.

Czuczman noted "[s]tandard induction or salvage chemotherapy regimens (including CHOP x 6) alone have previously been shown to be unable to clear bcl-2 positivity from marrow." EX1011, 003; EX1020, 009 ("Standard-dose CHOP alone" incapable of converting to *bcl-2* negativity). But CHOP was expected to offer favorable immunotherapy conditions and, unlike CHOP alone, the R-CHOP combination converted patients to *bcl-2* negativity. EX2029, ¶¶44-45, 62-63. In fact, Czuczman reported complete success with *bcl-2* clearance using R-CHOP: "[a]ll 4 [*bcl-2*-positive patients who completed treatment] converted to *bcl-2* negativity." EX1011, 003; *see also* EX1010, 009.

* * *

Again, in light of this remarkably-improved antitumor activity and "molecular complete remission with no detectable *bcl-2* rearrangement in marrow or blood by sensitive PCR methods," demonstrated by Czuczman's "well

tolerated" rituximab-plus-CHOP combination with "encouraging" toxicity data, POSITA reading Czuczman in 1999 would not have been motivated to replace CHOP with CVP, and thus risk losing those results by eliminating doxorubicin—the only CHOP component known to yield a particular benefit when combined with rituximab. EX1041, 003; EX1011, 003; EX1039, 003; EX2029, ¶64.

C. Petitioner Failed to Show POSITA Would Have Been Motivated to Replace CHOP With CVP

1. Beneficial Clinical Outcomes With Immunotherapy Combinations Were Uncertain and Unpredictable

As discussed above, Petitioner failed to show Czuczman teaches any chemoimmunotherapy beyond the specific R-CHOP combination. Likewise, none of Petitioner's other references ever discloses or proposes chemoimmunotherapy with CVP, much less where the immunotherapy is rituximab. EX2029, ¶¶65-69. To the contrary, the chemoimmunotherapy combinations in Foon (which Petitioner relies on for disclosure of CVP (Pet. 7-8)) involve immunotherapy combined with chemotherapy *other than CVP*: namely, regimens with combinations *including doxorubicin—i.e.*, IFN-α with CHOP-bleomycin or COPA (also called "mini-CHOP," which "uses the same drugs as CHOP given in reduced doses along with supportive agents, such as an antibiotic and an antifungal" (EX1059, 004)), or combining immunotherapy with *single agent chemotherapy* (*i.e.*, combining anti-idiotype antibodies and chlorambucil). *See* EX1008, 033-34; EX2029, ¶67. And

similarly, the immunotherapy disclosed in Dana, BCG, was *not combined with CVP*, but rather was given as maintenance therapy *after CHOP combinations* (including, *inter alia*, CHOP-BCG). *See* EX1009, 005 (Table 5); EX2029, ¶68. *See also* EX1002, ¶74 (distinguishing use *with* versus *following* chemotherapy).

Petitioner's erroneous assumption that POSITA would have been motivated to substitute *any* available chemotherapeutic agent for CHOP in Czuczman's highly-successful R-CHOP chemoimmunotherapy combination (*e.g.*, Pet. 51-52 (discussing IDEC)) is untenable. At the time of '821, it was unpredictable whether particular combinations with immunotherapies would even be *additive*, let alone *synergistic*, as Claim 1 requires. EX2029, ¶70. For example, among Foon's reported immunotherapy combinations, while IFN-α+CHOP-bleomycin yielded longer disease-free survival than historical CHOP-bleomycin results, combining IFN-α with COPA did *not* improve objective response rates over COPA alone. EX1008, 033; EX2018, 00003; EX2019, 00001; EX2029, ¶71. Similarly, combining two immunotherapies did not necessarily lead to additive *or even neutral* results in Foon: interleukin-2 (IL-2) combined with interferon-β "demonstrated *no activity* in patients with lymphoma"; and combining anti-idiotype antibodies with either IFN-α or chlorambucil did not improve the "50 percent response rate" achieved with anti-idiotype antibodies alone. EX1008, 033; EX2029, ¶72. Thus, of the immunotherapy combinations disclosed by Foon, four

of five (80%) failed to show even additive benefit—hardly a motivation that would support Petitioner's proposed alteration of Czuczman's highly-successful R-CHOP combination for *any* of Petitioner's challenges to claims 1-3. EX2029, ¶72.

2. The Petition Did Not Explain Why Selection of CVP to Combine With Rituximab Would Have Been Obvious From Among The Many Existing Agents

To argue POSITA would swap CVP for CHOP in Czuczman's R-CHOP (thus eliminating doxorubicin, *see supra* §V.B.2), Petitioner falsely portrays Foon and Dana as teaching only *two options*—CHOP or CVP—for combining with rituximab. Pet. 7-10. In doing so, Petitioner first ignores that (like Czuczman) *neither Foon nor Dana ever suggests combining rituximab with CVP*. EX2029, ¶¶73-74. Moreover, even if, *arguendo*, POSITA would have considered replacing CHOP in this combination, Petitioner ignores all of the known ***treatment agents other than CVP***, at least eleven of which are identified in Petitioner's Foon and Dana references (among other possibilities[14]) for combination with rituximab, including:

---

[14] Other Petitioner references note still more known chemotherapeutic agents for LG/F/NHL, including, *e.g.*, BACOP (EX1031, 007; EX1044, 007; EX1045; 003), BCVP (EX1046, 11), CIEP (EX1059, 004), and COPA (*id.*), and other references catalogued still more, like EVP (EX2001, 00001). EX2029 ¶74.

- at least **five** options for single-agent chemotherapy (*see* EX1008, 029 & Table 111-7; EX1009, 005-6 & Table 5):

    1) chlorambucil (and high dose pulsed chlorambucil),

    2) cyclophosphamide,

    3) fludarabine,

    4) pentostatin, and

    5) cladrabine.

- at least **six** combination chemotherapy regimens other than CHOP and CVP (*see* EX1008, 030; EX1009, 006), *e.g.*:

    1) COPP (and C-MOPP),

    2) ProMACE/MOPP,

    3) CHOP-bleomycin,

    4) CNOP,

    5) OAP, and

    6) BCNU+CVP.

EX2029, ¶74. Petitioner's expert conceded Foon disclosed at least thirteen chemotherapy options and Dana at least eight, and that there might be still more. EX2027, 46:21-48:23; 49:24-50:16; 44:9-18. But his declaration provided *no explanation* for plucking CVP from this universe. Instead, based on nothing but

hindsight from the '821, Petitioner inexplicably selected CVP from these many agents and presented it as the only alternative to CHOP.

Foon does not support this false binary choice. EX2029, ¶75. On the contrary, for various forms of "Low-Grade Lymphoma" Foon specifically identifies *other* chemotherapies:

- **Small Lymphocytic Lymphoma:** single-agent therapy ("generally . . . an alkalyating agent, such as **chlorambucil**"; "**fludarabine** and **cladribine** . . . are excellent second-line therapies"), or, for T-cell variants, "***[d]oxorubicin-based* regimens**" (*i.e.*, not CVP) or a single-agent ("**pentostatin** might be a reasonable alternative") (EX1008, 029; EX2029, ¶76);
- **Mucosa-Associated Lymphoid Tissue and Monocytoid Lymphomas**: "usually" single-agent therapy ("usually . . . an alkalyting agent") (EX1008, 029; EX2029, ¶77);
- **Follicular Small Cleaved Cell Lymphoma**: "**intensive regimens including *doxorubicin*"** (which "demonstrated *excellent responses*"[15];

[15] For example, Foon's reference 157 (EX1008, 030) reported better "[f]ailure free survival" with such intensive regimens (EX2025, 00003). Foon's reference 159 (EX1008, 030) taught an 81% complete remission (CR) rate in Stage III FL

EX1008, 030), various single-agents (including single-agent alkylating therapy such as **chlorambucil** or **cyclophosphamide**, and purine analogs such as **fludarabine**, **cladribine**, and **pentostatin**) as well as **CVP** (which displayed some advantages *over single-agent* alkylating therapy, but not significantly increased survival; *id*., 029-030; EX2029, ¶¶78-79); and

- **Follicular Mixed Lymphoma**: "we recommend . . . **CHOP**" and "[f]or patients who are not able to take doxorubicin, we recommend the **C-MOPP** or the **CNOP**" (EX1008, 030 (also noting potential *cure* with, *e.g.*, CHOP-bleomycin, C-MOPP, ProMACE/MOPP)); EX2029, ¶80.

Petitioner's reliance on Dana is similarly misplaced. In addition to omitting discussion of other clinical endpoints POSITA would find compelling (*see* §V.C.2(a), *infra*), Petitioner's statement from Dana that "addition of doxorubicin to CVP results in no improvement in survival" is not based even on a simple side-

---

patients, resulting in "prolonged remission and potential cure for over half of patients who achieved CR" with "moderate" toxicity, and noted the doxorubicin-containing regimen was "particularly encouraging for those with follicular small cleaved and mixed histologies." EX2026, 00003; EX2029, ¶78.

by-side comparison of CHOP and CVP, as Petitioner misleadingly suggested. EX1009, 006; Pet. 7-10; *see* Dec. 22-23, 27; EX2029, ¶82. Dana retrospectively considered patients from three clinical trials who were given what was generally described as "doxorubicin-based therapy" (EX1009, 008), and reported median survival of approximately 7 years. EX1009, 004; EX2029, ¶82. Dana's researchers then looked to an unrelated study (EX1044) to draw a rough comparison, observing simply that Dana's 7-year survival with CHOP-containing regimens was "comparable to those achieved with" three other therapies in this separate study—*i.e.*, single-agent chlorambucil, CVP, and CVP+total lymphoid irradiation. EX1009, 006; EX2029, ¶83. Dana does not state, and Petitioner provides no prove its "doxorubicin-containing treatments" were CHOP-only treatment. In any event, merely suggesting *equivalence* between CHOP alone and CVP alone in overall survival (*i.e.*, *no advantage* for CVP alone; *see* EX1002, ¶111 (survival rates "indistinguishable")), would not have motivated POSITA to remove CHOP from Czuczman's successful combination (particularly given POSITA's understanding of the benefits of R-CHOP's doxorubicin component, *supra*, §V.B.2), and to substitute CVP (lacking doxorubicin). EX2029, ¶¶45-48; 58-64; 83-84.

While Petitioner's expert asserts POSITA would have been motivated to find a "chemotherapy regimen that was less toxic but equally effective" as R-

CHOP (EX1002, ¶108), Petitioner fails to show how these two separate requirements would have been met by CVP. EX2029; ¶85. Indeed, in view of Czuczman's 100% response rates, *bcl-2* clearance, and encouraging toxicity data achieved with CHOP-plus-rituximab in LG/F-NHL, POSITA starting with Czuczman's regime would have had *no basis* to reasonably predict this goal could be achieved, or how, with CVP, which was understood to be less effective than CHOP. *E.g.*, EX2029, ¶¶86-89; EX2027, 40:2-19.

(a) Petitioner Failed to Show POSITA Would Have Expected R-CVP and R-CHOP to be "Equally Effective"

Petitioner failed to establish POSITA would have expected R-CVP to be at least "equally effective" as R-CHOP. EX2029, ¶85. *Cf.* EX1002, ¶108. Czuczman affirmatively disclosed multiple improved clinical outcomes for the R-CHOP combination: molecular complete remission and 100% response rates, accompanied by "encouraging" toxicity data. *E.g.*, EX1041, 003; EX1039, 003 ("well tolerated"); EX1011, 003 (no "unexpected toxicities"); EX2029, ¶¶86-87. Before altering this successful therapy, POSITA would have needed, *inter alia*, an expectation that an alternative agent would yield more favorable results. EX2029, ¶¶86-87. As noted above, Foon and Dana discuss superior outcomes in LG/F-NHL patients on a variety of clinical endpoints with intensive chemotherapy regimens like CHOP. While these references include overall survival as *one* clinical

endpoint, POSITA would not have based selection of a chemotherapy agent—and certainly not an agent to replace Czuczman's remarkably-successful R-CHOP therapy—on this single endpoint *to the exclusion of other endpoints*. See EX2027, 27:25-28:13 (conceding "multiple components" to efficacy). This is particularly so where –as Petitioner urges—there was *no difference* between the agents on that endpoint. Pet. 9; EX2027, 38:20-24, 90:11-18; EX1002, ¶111; EX2029, ¶88; *cf.* EX2027, 28:14-29:19. Tellingly, neither Foon nor Dana indicate whether CVP is at least equally effective as CHOP (let alone R-CHOP) on the specific endpoints highlighted by Czuczman as remarkable successes, including molecular complete remission and 100% response rates. EX2029, ¶85. Furthermore, Petitioner has not shown why single-agent therapy (*e.g.*, with chlorambucil, cyclophosphamide, fludarabine, pentostatin, cladrabine, or high dose pulsed chlorambucil) in Foon and Dana, would not have been deemed *better* than CVP for expected efficacy. In fact, Dana compares long-term survival on doxorubicin-based therapy with "*single agent[]*" therapy like chlorambucil, confirming single-agent therapy was being considered by POSITA looking at survival. EX2029, ¶89. Similarly, fludarabine was identified in Foon as an effective single-agent chemotherapy for LG/F-NHL with similar survival rates as CVP therapy. EX1008, 029; EX2029, ¶¶81, 89. Furthermore, Petitioner's EX1044 discloses relapses remained high for both CVP and single agents. *Id.* 006. Thus, without any further indication about meeting or

exceeding Czuczman's remarkable results in terms of molecular complete remission and response rates (*cf*. EX1002, ¶108 (conceding candidates would need to be at least "equally effective")), POSITA would have had no reason to replace CHOP, or choose CVP over single-agent alternatives[16] in the unlikely event of even considering a replacement of CHOP in R-CHOP. EX2029, ¶89.

(b) Any Alleged Toxicity Differences Between CHOP and CVP Would Not Have Motivated POSITA to Replace CHOP With CVP in R-CHOP

(i) R-CHOP Was Well Tolerated

Petitioner's toxicity argument rests on a false assumption about R-CHOP's toxicity that ignores Petitioner's own primary reference: Czuczman reported R-CHOP "is *well tolerated* and adverse events do not appear to exceed those expected with CHOP alone." *See, e.g.*, EX1017, 003; EX1039, 003; EX1020, 002, 009 ("no significant added toxicity"); EX1049, 003 ("minimal additional toxicity"); EX2029, ¶90. Thus, POSITA would certainly not have considered replacing CHOP with an agent like CVP on this basis alone. *See supra*, §V.B.2; EX2029, ¶90.

[16] Fludarabine's proposed mechanism of action, for example, was thought to be different from CVP's or CHOP's. EX1008, 030; EX2029, ¶89 .

(ii) POSITA Would Have Had No Motivation To Replace CHOP With CVP for Toxicity Reasons

To satisfy the second requirement of Petitioner's two-part argument for obviousness (efficacy *and toxicity*, *see* EX1002, ¶108; Pet. 51), Petitioner suggested POSITA might have substituted CVP for CHOP because "[a] POSA would have understood from Foon and Dana that CVP was a standard chemotherapy regimen that was *less toxic* but equally effective as CHOP for low-grade NHL." Pet. 51. But Petitioner's evidence does not support this. *See*, *e.g.*, EX2027, 53:13-55:14 (conceding Petitioner's cited "toxicity" evidence doesn't compare CVP), 9:22-25 (Lossos conceding *he* has treated LG/F-NHL *with CHOP*), 40:20-41:7 (others "use[d] CHOP rather than CVP"), 40:2-19, 62:18-63:13; EX2029, ¶94. Czuczman makes no mention of CVP, and confirms R-CHOP had no "unexpected toxicities." *E.g.*, EX1011, 003; *see also* EX1041, 003 ("Current efficacy and toxicity data appear encouraging"). Foon nowhere addresses the relative toxicities of CVP and CHOP; Foon merely discusses "intensive combination regimens including doxorubicin." EX1008, 030; EX2029, ¶94-95. The Petition never demonstrated "intensive" equates with "more toxic." On the contrary, Foon's cited reference 159 (EX2026), notes "[t]oxicity was *moderate*" with its intensive doxorubicin-containing regimen (CHOP-Bleo), consistent with Foon's confirmed tolerance of CHOP-containing regimens. EX2026, 00003. Nor

does Dana compare toxicities. EX1009; EX2029, ¶96-97. In fact, Dana does not address toxicity *at all*—it simply reviews survival data. *Id.*, 002; EX2027, 61:15-20; EX2029, ¶¶82-83; 96. Furthermore, Petitioner's EX1044 (Abstract, Table 3) confirms each of cyclophosphamide and chorambucil were less toxic than CVP when it came to "[a]cute complications of therapy," thus pointing to single-agent therapy, rather than CVP, if toxicity were a driving concern. EX2029, ¶98.

Furthermore, even if—notwithstanding R-CHOP's clear benefits and "encouraging" toxicity (*e.g.*, *supra* §§V.B.2, V.C.2(b)(i); EX1041, 003; EX1011, 003)—POSITA would have been motivated to seek a "less-toxic" alternative to substitute into Czuczman's highly-successful R-CHOP regimen (for the reasons above, this is not the case), Petitioner has not shown POSITA would have chosen CVP.

(1) Petitioner Failed to Show POSITA Would Have Understood a Full Course of CVP Treatment to be Less Toxic

While Petitioner suggested toxicity as a motivating factor in replacing CHOP, Petitioner failed to show POSITA, at the time of '821, would have understood a treatment *with enough CVP to achieve appropriate efficacy against LG/F-NHL* to be "less toxic" than CHOP. Although the Petition tellingly omitted this, Petitioner's expert now admits the comparative toxicity of CVP and CHOP depends on dosage, particularly of the cyclophosphamide. EX2027, 27:9-24. This

is particularly revealing given that Petitioner's EX1036 (Bishop), indicates durable responses, including in LG-NHL, required not just *ordinary* CVP but, rather, *"high dose"* CVP (with 1500 mg/m^2 cyclophosphamide), resulting in toxicity, including neutropenia, hematological toxicity, and significant infections. *See, e.g.*, EX1036, 002, 005; EX2029, ¶93; *see also* EX2027, 27:9-24. Thus, Petitioner failed to prove even its first premise for obviousness: it did not show POSITA would have understood and expected the R-CVP needed to achieve a durable response would have lower overall toxicity than R-CHOP. EX2029, ¶93

(2) Even POSITA Assumed to be Motivated by Toxicity Would Have Considered Agents With Higher Efficacy

Moreover, even (1) ignoring Czuczman's express teaching that R-CHOP was "well tolerated" (EX1039, 003; *see supra* §V.C.2(b)(i)); (2) assuming a difference in the perceived toxicities of CHOP and CVP in the context of actually treating LG/F-NHL (*cf. supra* §V.C.2(b)(ii)(1)); and (3) assuming Petitioner had shown any such difference would have motivated POSITA to alter Czuczman to eliminate doxorubicin (*cf. supra* §V.B.2), Petitioner has ignored other chemotherapeutic agents with toxicities perceived to be equivalent to or lower than CVP's, but *with higher efficacy* than CVP in particular clinical outcomes (such as higher remission rates), were available and known. For example, chlorambucil, an alkylating agent identified in, *e.g.*, Foon and Dana, had been considered a

treatment of choice for LG/F-NHL patients. EX1008, 029; EX1009, 005; EX2029, ¶100. This drug, used alone or in combination with prednisolone, was known to induce a 70% objective regression rate with an approximate 30% CR rate in newly-diagnosed FL patients while leading to a very low rate of general toxicity. *See*, *e.g.*, EX2023, 00004; EX2020, 00002-3; EX2029, ¶100; *see also* EX2022, 00003. Assuming, *arguendo*, POSITA would consider a chemotherapeutic alternative to CHOP in R-CHOP based on perceived lower toxicity, they would have considered chlorambucil (which is milder than CVP for toxicity, EX2022, 00003) or fludarabine, not CVP. EX2029, ¶100-101.

Petitioner's McNeil article, although in the context of intermediate-grade NHL, similarly identified several "drug combinations"—none of which is CVP, and none in combination with rituximab—"that may be as effective but less toxic than CHOP." EX1059, 004. These included "CIEP, in which the less toxic idarubicin and VP16(P) are substituted for CHOP's doxorubicin and vincristine," and "mini-CHOP," called COPA. EX1059, 004. McNeil reported "[p]reliminary data . . . suggest that outcomes [for mini-CHOP] are similar to CHOP in the elderly with less chance of side effects." *Id.*; EX2029, ¶102. Tellingly, Petitioner completely ignored this disclosure, which confirms, even if POSITA were assumed to have toxicity concerns about CHOP and a motivation to alter Czuczman's R-CHOP (POSITA wouldn't), POSITA would, *inter alia*, use mini-CHOP to address

those concerns, not CVP, especially given doxorubicin's known benefit with rituximab. EX2029, ¶102.

Finally, in addition to ignoring these less-toxic alternatives from Petitioner's own exhibits, Petitioner also failed to address its asserted toxicity concerns *together with the requirement of efficacy its own expert concedes is necessary for all of its obviousness combinations*. *See* EX1002, ¶108 (arguments rest on premise of "chemotherapy regimen that was less toxic *but equally effective*"). The reason is simple: as detailed in §§V.B.2 & V.C.2(a), POSITA would not have understood or expected R-CVP to meet the remarkable efficacy measures reported by Czuczman for R-CHOP.[17] EX2027, 40:2-19; EX2029, ¶¶99, 104.

[17] Petitioner similarly ignores that the addition of rituximab to chemotherapy combinations gave some researchers hope they could increase overall patient survival. For those researchers, accepting what might be slightly more toxicity was considered a worthwhile tradeoff, since the results of R-CHOP were so favorable. *See* EX2027, 26:7-12 (Lossos: "Once again, we can give any chemotherapy that will be less toxic but will not be as effective or efficient. . . There are medications that are less toxic, but they are not effective"), 95:14-96:2 (finding LG-NHL treatment useful based on *response rates*: "we are speaking about somebody that doesn't have a lot of options, is going to die, and if we will

3. Petitioner's Other "Prior Art" Does Not Provide a Motivation to Replace CHOP With CVP

Petitioner's reliance on Marcus (EX1005), Maloney (EX1022), Steward (EX1031), and McNeil (EX1059) is also misplaced:

- Marcus cannot be considered for claims 1-3 (and thus with Petitioner's argued modifications to Czuczman), because the Board *excluded* Marcus from institution against those claims after properly determining Petitioner failed to show they were not entitled to the '202 Application's filing date. Dec. 13.
- Maloney nowhere addresses CVP, let alone its toxicity. EX1022; EX2027, 56:19-22. Maloney concludes R-CHOP's toxicity "appeared to be comparable to that observed with the antibody alone and that expected from treatment with CHOP" (EX1022, 011), confirming the combination yielded no additional toxicities.

---

achieve…a duration of response within three or four months, that may be meaningful"). For researchers who, in contrast, believed choice of treatment would not impact overall survival, there was no similarly compelling reason to combine rituximab with any chemotherapeutic options to begin with. EX2029, ¶103.

- Steward refers to studies of numerous alternatives to "the use of combination chemotherapy (predominantly CVP) and single alkylating agents (chlorambucil or cyclophosphamide)," and generally concludes "[u]nfortunately these studies . . . ***often*** have resulted in more toxicity," but without comparing any particular agents directly. EX1031, 007; EX2027, 57:17-58:16.
- McNeil nowhere addresses CVP, let alone compares its toxicity to CHOP's. EX1059; EX2027, 56:23-57:14.

Moreover, none of these have been shown to be a prior art printed publication. *See supra* §IV.

D. POSITA Would Not Have had a Reasonable Expectation of Success in Combining CVP and Rituximab

"[P]harmaceutical development is an unpredictable art." *Mylan Pharm. Inc. v. Yeda Research & Dev. Co.*, IPR2015-00643, Pap. 90 (FWD), 19 (Dec. 2, 2016); *In re Efthymiopoulos*, 839 F.3d 1375, 1380 (Fed. Cir. 2016) ("medicinal treatment" is "unpredictable art[]"). For many of the same reasons POSITA would *not* have been motivated to substitute CVP for CHOP in Czuczman's remarkably-successful R-CHOP—even applying, *arguendo*, Petitioner's stated test of achieving a "regimen that was less toxic but equally effective" as R-CHOP (EX1002, ¶108)—Petitioner also fails to establish a *reasonable expectation of success in doing so* in

this unpredictable art. EX2029, ¶106. *See, e.g.*, *supra*, §V.C.1 (explaining "Beneficial Clinical Outcomes with Immunotherapy Combinations Were Uncertain and Unpredictable").

To suggest CVP would be "equally effective" in the eyes of POSITA reading Czuczman, Petitioner and Dr. Lossos would have needed to start with Czuczman's reported R-CHOP results—including (1) 100% overall response rate, and (2) complete conversion to *bcl-2* negativity (EX1011, 002). They would then have had to show POSITA would reasonably have expected substituting CVP would achieve the same or better results. EX2029, ¶107. But instead, they *ignored* these two clinical outcomes altogether, and suggested overall survival *alone* would have dictated substitution of CVP for CHOP in Czuczman. However, Czuczman does not even mention overall survival. And, at best, Petitioner's evidence suggests "*no difference" between CVP and CHOP*.[18] Pet. 9-10; EX2027,

[18] Petitioner's references did not suggest CVP would achieve superior survival compared with other options, including CHOP. *See, e.g.*, EX1002, ¶¶40 (Lossos: "*similar* survival rates" for CHOP and CVP), 111 (Lossos: CVP's "survival…rates indistinguishable from CHOP"). Foon merely reported CVP did not have significantly longer overall survival rates compared with single-agent alkylating therapy, and for "intensive combination regimens including doxorubicin," there

38:20-24 (Lossos' opinion: "no difference in survival"); EX2029, ¶107. No POSITA, of course, would have considered CVP "equally effective" (EX1002, ¶108; Dec. 27) if it displayed "equality" in only one measure of efficacy, and fell short in other significant dimensions like those highlighted by Czuczman, and ignored by Petitioner. EX2029, ¶109; *cf*. EX2027, 27:25-28:12 ("multiple components" of efficacy). But that is precisely the record Petitioner presented: *None* of Petitioner's references discussed molecular conversion to *bcl-2* negativity with CVP, let alone provided any reason POSITA would expect CVP to lead to molecular complete conversion if swapped for CHOP. EX2029, ¶111. And *none* suggested a 100% overall response rate for CVP, let alone gave POSITA any reason to expect CVP would achieve this if substituted for CHOP in R-CHOP. EX2029, ¶111. Indeed, as discussed in §V.B.2, POSITA would have understood the only known beneficial results from combining a CHOP component with rituximab came from *doxorubicin, which CVP eliminates*.[19] Clearly POSITA,

---

was "no evidence that such treatment *prolongs* survival." EX1008, 030; *see* Dec. 22-23; EX2029, ¶81. Dana reported likewise. EX1009, 006; *see* Dec. 22-23; EX2029, ¶82.

[19] Similarly, Petitioner's invocation (Pet. 53-54) of Czuczman's rationale for experimenting with R-CHOP –including Demidem's sensitization of CHOP's

knowing this and starting with Czuczman, would not have had any reasonable expectation that replacing CHOP with CVP would have been "equally effective" for overall response rates and molecular conversion to *bcl-2* negativity. EX2029, ¶110.

Rather than compare efficacy on the measured clinical outcomes that would have caused POSITA to start with Czuczman's R-CHOP (*e.g.*, overall response rate and molecular conversion to *bcl-2* negativity), Petitioner and its expert searched instead for other possible "efficacy" metrics to justify the result they wished to prove. But even so, the actual data fail to support Petitioner's arguments.

For example, although Dr. Lossos has now admitted CHOP achieved *better* efficacy than CVP (EX2027, 40:2-19), he originally implied equivalence in clinical response rates for CVP and CHOP. *See, e.g.*, EX1002, ¶¶40, 111 (arguing CVP had "*response rates* indistinguishable from CHOP"). But in support, he compared apples with oranges and then cherry-picked comparison data for clinical endpoints and patients. Lossos later conceded not knowing the patient population studied in

---

doxorubicin component with rituximab (*see infra* §VI.B)—would not have led POSITA to any expectation of success with CVP, which *lacked* doxorubicin. EX2029, ¶111

some of these studies, and acknowledged not all the studies were directly comparable. EX2027, 69:22-70:3; 77:12-23. Rather than comparing the same endpoints, Dr. Lossos reported a scattering of results for CVP and CHOP, but across *different types of response rates*— such as *initial* response rates for CVP (which he reports as 75-90%) and *partial* response rates for CHOP (which he reports at 60%). EX1002, ¶40. He then suggested these show that response rates for CVP and CHOP were similar. *See, e.g.*, EX1002, ¶40 (connecting various CVP results and various CHOP results on different response measurements with "Similarly"); *see also id*. at ¶111 ("indistinguishable"). These data on different measures, of course, suggest nothing of the kind. EX2029, ¶112.

The references Dr. Lossos cites do include some data for both CVP and CHOP on the same measurements, but they include findings that *conflict* with his assertions. EX1029, ¶112. For example, Canellos (EX1045, 005) reports only "approximately *50%* of patients will achieve a complete remission of all measurable disease" with CVP, while Dr. Lossos asserted this number was *60%* (higher) for CHOP. EX1002, ¶40 (citing EX1047, 003). This does not support Petitioner's argument that POSITA would expect at minimum "equally effective" results by substituting CVP in Czuczman's combination. *See also* EX2027, 40:2-19; EX2029, ¶115. And while Dr. Lossos also cited Steward as reporting "CVP induced complete remission in 57% of patients with low-grade NHL"

(EX1002, ¶40), Steward's treatment involved a *3-stage therapy* of: (1) CVP followed by (2) radiotherapy to sites of previous bulk disease, and then (3) either (a) no additional treatment or (b) maintenance chemotherapy with 2 years of intermittent chlorambucil (EX1031, 003). EX2029, ¶113.

Dr. Lossos also ignores the particular patients treated in presenting his supposedly "comparative" CHOP data. For example, for CHOP figures Dr. Lossos selected a study (Kimby) whose patient population had *advanced Stage III or IV symptomatic LG-NHL* and thus "no other treatment alternative" (EX1002, ¶52), thereby producing lower complete remission rates "because of residual bone marrow disease." *See* EX1047 (cited in EX1002, ¶40), 003, 005; EX2029, ¶115. As any POSITA would recognize, Lossos clearly cherry-picked references, with the benefit of hindsight, in an attempt to suggest CVP results in better response rates than CHOP. EX2029, ¶114. In fact, a closer inspection of those references, including the patients treated, reveals they cannot support his conclusions about expectations of equivalent efficacy based on similar response rates. *See* EX2029, ¶116; EX2027, 69:22-70:3; 77:12-23, 81:9-85:9. And contrary to Lossos' original testimony, POSITA knew CHOP could, *inter alia*, increase "complete remission

rates" compared with CVP. EX1047, 003, 007; EX1005, 003; EX2029, ¶115; *see also* EX2027, 40:2-19.[20]

In sum, the Petition failed to establish POSITA starting with Czuczman would have had any reasonable expectation of success in achieving "equal efficacy" by substituting CVP for CHOP.

VI. POSITA WOULD NOT HAVE REASONABLY EXPECTED REPLACING CHOP WITH CVP IN R-CHOP WOULD YIELD A "BENEFICIAL SYNERGYSTIC EFFECT"

A. "Beneficial Synergist Effect" Requires an Effect Better Than the Additive Effects of Each Agent

Claim 1 describes a method of administering rituximab during a CVP regimen "wherein the method provides a beneficial synergistic effect in the patient." But Petitioner failed to explain how Czuczman (EX1011), in view of Foon (EX1008) and Dana (EX1009), teaches "a beneficial synergistic effect" *as in claim 1*. Nor did Petitioner's expert even consider this definition from the '821, despite recognizing it. EX2027, 32:1-20. Petitioner relies *solely on Czuczman* for

[20] Indeed, particularly given Czuczman's successes, Petitioner has not shown why POSITA would not have selected "intensifications" (*e.g.*, PROMACE-MOPP) instead of CVP (EX1009, 168) if "equally *effective*" treatment were desired. EX2029, ¶105.

this limitation (*e.g.*, Pet. 46, EX1002, ¶¶103, 104), but while Czuczman contains the word "synergy," Czuczman fails to disclose a "beneficial synergistic effect" as properly construed. *See* Dec. 7; *supra* §III.A.

Invalidity analysis requires more than a word-search. *Google Inc. v. Intellectual Ventures II LLC*, 701 F. App'x 946, 953 (Fed. Cir. 2017) (anticipation analysis required more than "word search" for pertinent term). As detailed below, because Czuczman does not teach any "beneficial synergistic effect" as required by claim 1—and Foon nor Dana don't, either—even if there were a motivation to combine these references (there isn't), Petitioner failed to provide any disclosure of the required "beneficial synergistic effect."

B. The Combination of Czuczman, Foon, and Dana Does Not Disclose a "Beneficial Synergistic Effect" for CHOP Plus Rituximab

Petitioner alleges Czuczman teaches a "beneficial synergistic effect" because it describes (1) all patients who completed the therapy having either complete or partial responses; and (2) a *bcl-2* conversion rate as "superior to CHOP therapy alone" and, according to Petitioner, states rituximab exhibits "synergy with chemotherapeutic agents." (Pet. 45-46). But Petitioner's analysis applies the wrong construction: to disclose the claimed "beneficial synergic effect," Czuczman must disclose a clinical outcome from combination therapy that reflects a beneficial effect *greater than the additive effects of (a) rituximab alone*

and (b) CHOP alone. But Czuczman does not do so: all 14 patients completing scheduled therapy in the study received *only the combination therapy*: *no* patient received CHOP alone, and *no* patient received rituximab alone. EX2029, ¶¶117-125. Nor, as discussed below, did Czuczman report outcomes for such treatments that would allow POSITA to compare its results with the additive results. EX2029, ¶118. Thus, Czuczman—the Petition's only argued source of evidence for this disclosure—fails to disclose Claim 1's "beneficial synergistic effect." In particular:

- ***Response Rates:*** Czuczman discloses response rates only for (a) R-CHOP but not (b) rituximab alone or (c) CHOP alone. Thus, POSITA could not determine from Czuczman whether the combination's response rate is better than the additive effects of CHOP and rituximab alone. EX1011, 003; EX2029, ¶119.
- ***Bcl-2 Conversion:*** Again**,** because Czuczman does not disclose *bcl-2* conversion rates for rituximab alone, POSITA would not be able to determine from Czuczman whether the conversion rate for the combination therapy is better than the additive effects of each single therapy. EX1011, 003; EX2029, ¶120.

While Czuczman briefly mentions "synergy with chemotherapeutic agents" as a "rationale for combination of IDEC-C2B8 with CHOP" (EX1011, 003), this

abbreviated comment (1) did *not* concern the actual findings reported in Czuczman, and (2) was *not* a disclosure of clinical outcomes from combination therapy that reflect a greater beneficial effect than the additive effects of the uncombined therapies administered alone.[21] EX2029, ¶121. Far from disclosing a more-than-additive benefit to actual patients *in vivo* from *combined* treatment with rituximab, the phrase "synergy with chemotherapeutic agents" in Czuczman refers to earlier *in vitro* (not *in vivo*) experiments by Demidem (EX1078, cited in Czuczman as "FASEB J. 9:A206, 1995") that evaluated the ability of rituximab to "sensitize" cell lines to certain chemotherapeutic agents, including by "pre-treatment." EX1041, 003; EX1079, 008 (Table 2); EX2029, ¶122. But Demidem

[21] Respectfully, as discussed above, the Board's statement that "Czuczman taught that rituximab exhibits 'synergy with chemotherapeutic agents,' without describing any limitation on the type of chemotherapy, such as requiring it to include doxorubicin like CHOP" (Dec. 24), is not supported by Czuczman or by the Demidem reference Czuczman cites in connection with this comment about a "synergy" rationale for combining rituximab and CHOP. Nor does the Board's institution decision cite to any discussion in the Petition of the "beneficial synergistic effect" limitation; instead, it cites Petitioner's motivation to combine and reasonable expectation of success arguments. *See id*. (*citing* Pet. 51-54).

(EX1078) does not use the word "synergy" even once, and even Petitioner's expert now concedes Demidem does *not* teach synergy under the proper construction. EX2027, 89:4-13.[22]

Moreover, even with respect to Demidem's discussion of "sensitization," Demidem does not disclose or discuss sensitization to *all* chemotherapeutic agents, and never mentions sensitization to *any* component of CVP. *See* EX1078. Indeed, an additional Demidem paper proffered by Petitioner further confirmed rituximab did *not* sensitize lymphoma cells *in vitro* for *all* chemotherapeutic agents; it sensitized cancer cells to cisplatin *and doxorubicin* (a.k.a. Adriamycin), but not etoposide. EX1079, 008; EX2029, ¶123. As any POSITA would have recognized from these documents, the Demidem authors did not test C, V, or P in their sensitization assay; nor did they test each chemotherapy agent (or rituximab) on its own to determine whether the sensitization observed after pre-treating cells with

[22] Petitioner's expert originally suggested Demidem's EX1079 disclosed "synergistic effects" (EX1002, ¶68; *see also id*. ¶33), but later testified *in vitro* data is required to determine synergy under the Board's construction and that Demidem's *in vitro* data in EX1078 (cross-referenced in EX1011) and EX1079 was insufficient. Further, neither EX1078 nor EX1079 discloses any *in vivo* data related to the combination of CHOP or doxorubicin and rituximab.

rituximab was better than additive effects of each agent alone. EX2029, ¶124. Neither Demidem reference discusses any clinical outcomes resulting from combining rituximab with chemotherapy (much less CVP or CHOP), or whether any such outcomes were better than the additive effects of each single agent by itself. In fact, the Demidem references do not discuss *any in vivo* clinical outcomes at all. Thus, the Demidem references do not and could not disclose a "beneficial synergistic effect." EX2029, ¶¶122-125; *see also* EX2027, 89:4-13. And because Czuczman cites only Demidem in referring to its "synergy with chemotherapeutic agents" rationale for experimenting with R-CHOP, even if Demidem is considered Czuczman fails to provide the required disclosure.[23]

[23] To the extent Petitioner hopes to suggest Czuczman's shorthand reference to a "synergy" rationale would somehow have changed POSITA's understanding of the actual statements underlying it—including cited Exhibits 1078 and 1079 (elaborating upon 1078), both known to any POSITA—this is nonsense. *See Genzyme Corp. v. Dr. Reddy's Labs., Ltd.*, No. 2016-2206, 2017 WL 6418934, at *3-4 (Fed. Cir. Dec. 18, 2017).

C. Neither Foon Nor Dana Discloses a "Beneficial Synergistic Effect" for R-CHOP

As noted above, neither Foon nor Dana teaches any synergistic effect between rituximab and any chemotherapy agent (and the Petition never suggests either does so). EX2029, ¶126. The word "synergy" is never used in either document, and neither contemplates any combinations with a chemotherapeutic agent and rituximab. Thus, neither Foon nor Dana discloses the missing "beneficial synergistic effect" required by claim 1. EX2029, ¶126.

VII. THE CHALLENGED CLAIMS ARE ENTITLED TO THE BENEFIT OF AT LEAST AN AUGUST 11, 1999 PRIORITY DATE

The Board correctly found at institution, and again in denying Petitioner's Request for Rehearing, that the limitations in claims 1-3 are supported by the '202 Application, and the priority of those claims is not at issue here. Dec. 10-11; Pap. 25, 8-10.[24] However, Petitioner respectfully submits that, contrary to the Institution Decision, claims 5-6 are also entitled to the August 1999 priority date.

[24] None of the claim 1-3 instituted grounds depends on determining whether they are entitled to a 1999 priority date (as PO asserts) or a 2012 date (as Petitioner asserted). Therefore, this issue need not be decided for the claim 1-3 arguments. *E.g., Genband US LLC*, IPR2015-01457, Pap. 38 (FWD), 19 (Dec. 15, 2016) (declining to reach unnecessary issue).

The difference between claims 2 and 3, and claims 5 and 6, respectively, is that claims 5 and 6 require eight cycles with 375 mg/m^2 of R-CVP, spaced three weeks apart. *See, e.g.*, Pet. 28-30; Dec. 11-12. Petitioner thus identified support for claims 1-3 (and the corresponding limitations in claims 5-6) for completeness of the record, followed by support for the additional specific limitations of claims 5-6.

The '821 claims priority through continuations to the August 11, 1999 '202 Application. Petitioner's meritless assertion that the claims lack support in the '202 (Pet. 19) recycles arguments addressed and rejected during prosecution. *See, e.g.*, EX1069, 126; Pet. 21.

A. Petitioner Bears the Burden of Persuading the Board That the '821 is Not Entitled to the Benefit of its Priority Date

Contrary to Petitioner's assertion (Pet. 20), PO, at most, bears a burden of production on priority. *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008); *id.* at 1329. It remains Petitioner's burden to persuade the Board that PO "is ***not*** entitled to the benefit of the earlier filing date." *Id.* at 1328; *HTC Corp. v. Advanced Audio Devices*, LLC, IPR2014-01158, Pap. 36 (FWD), 10-11 (Jan. 22, 2016); *Microsoft Corp. v. Raniere*, IPR2016-00669, Pap. 11, 7 (Nov. 10, 2016).

B. The '202 Application Discloses the Inventor Had Possession of Administering Rituximab During a CVP Regimen to Treat Low-Grade B-Cell NHL, Including With Synergistic Effect.

Under §112, ¶1, "the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

"The 'written description' requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way." *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005); *see id.* at 1357. "[T]he written description requirement does not demand either examples or an actual reduction to practice," and it "does not demand any particular form of disclosure, or that the specification recite the claimed invention *in haec verba*." *Ariad*, 598 F.3d at 1352; *Apple Inc. v. Papst Licensing GMBH & Co. KG*, IPR2016-01844, Pap. 10, 20 (Mar. 10, 2017); *In re Herschler*, 591 F.2d 693, 700-701 (C.C.P.A. 1979); *see also All Dental Prodx, LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002) (quoting *Eiselstein v. Frank*, 52 F.3d 1035, 1038–39 (Fed. Cir. 1995)). "[Even] the failure of the specification to specifically mention a limitation that later appears in the claims is not a fatal one when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented." *Id.* at 779.

The written description requirement is satisfied "when 'the essence of the original disclosure' conveys the necessary information – 'regardless of *how* it' conveys such information." *Inphi Corp. v. Netlist, Inc.*, 805 F.3d 1350, 1354 (Fed. Cir. 2015).

1. The Challenged Claims Are Entitled to the Benefit of the '202 Application's Filing Date

As the Board correctly found at institution (Dec. 10), it is undisputed that original claim 17 in the '202 Application recites "[a] method for treating B-cell lymphoma comprising administering to a patient a therapeutically effective amount of anti-CD20 antibody before, *during* or subsequent to *a chemotherapeutic regimen*." EX1034, 058; *id*. 009; Pet. 22. Thus, the '202 Application expressly described administering immunotherapy "during" a chemotherapeutic regimen. *See also* EX1034, 008-9; Dec. 10-11. And, as the Board found and the Petition concedes (Dec. 10-11; Pet. 22-23), the '202 Application, in related disclosures, describes the various elements of the method of the Challenged Claims, including the immunotherapy (rituximab), the chemotherapeutic regimen (CVP), and the type of B-cell lymphoma (LG/F-NHL) for which the combination of chemotherapy and immunotherapy may be used.

Low–grade/follicular NHL. The '202 describes, for example, that LG/F-NHL is a B-cell lymphoma for which the claimed combination therapy may

be used: it is undisputed that original claim 29 depends from claim 17 and describes "low grade/follicular" NHL as a subtype of B-cell lymphoma that can be treated with the method of claim 17. EX1034, 061; Pet. 23; Dec. 10-11. The Application also disclosed that "[t]he methods of the present invention may be used to treat a variety of B-cell lymphomas, including low grade/follicular non-Hodgkin's lymphoma (NHL)…" EX1034, 010-011.

CVP. The '202 Application further disclosed CVP as a chemotherapeutic regimen used in the claimed invention, including in original claim 17. For example, the application disclosed such use of CVP in connection with describing a study of patients with low-grade NHL, referring to "standard CVP therapy." EX1034, 032; Pet. 25-26; Dec. 10-11; *see also* EX1034, 029 (describing COP (*i.e.*, CVP) regimen for treating CLL). And, Dr. Lossos himself acknowledged POSITA would have known that CVP was standard chemotherapy for lymphomas. EX1002, ¶¶65, 85 ("CVP was a standard therapy for lymphoma"), 101 ("CVP was a well-known standard chemotherapy treatment"), 108.

Rituximab/C2B8/Anti-CD20 Antibody. The '202 Application disclosed that "any anti-CD20 antibodies can be used for the methods of the present invention," and expressly stated that "a preferred chimeric antibody is *C2B8* (IDEC Pharmaceuticals, *Rituximab*[])." EX1034, 006-007; *see also* Dec. at 9-11. Further, as the Petition concedes, "[o]riginal claim 20, which depends from claim

19, which depends from claim 17[,] recites use of the chimeric antibody C2B8 (rituximab) in the method of claim 17" (Pet. 24), and rituximab is an anti-CD20 antibody. Pet. 40 ("*rituximab*—a specific chimeric *anti-CD20 antibody* also known as *C2B8*"); EX1034, 005 ("anti-CD20 antibodies and, in particular…*Rituximab*[]").

Thus, these related disclosures together teach treating LG/F-NHL by administering rituximab during a chemotherapy regimen consisting of CVP therapy.

Beneficial synergistic effect. Finally, with respect to claim 1 (*see* n.24, *supra*), the '202 Application discloses "treatment with anti-CD20 antibody provides a beneficial synergistic effect when administered in combination with . . . chemotherapy." EX1034, 026; Pet. 26; Dec. 10-11. This disclosure shows the inventors understood that combining chemotherapy and rituximab provides a beneficial synergistic effect. Certainly nothing in the Application restricts the immunotherapy/chemotherapy combination from using CVP or negates the '202 Application's CVP disclosures, including, *e.g.*, its express disclosure of standard CVP therapy. Dec. 10-11. Indeed, the Petition's argument that disclosure of the beneficial synergistic effect must "make[]…specific reference to a beneficial, synergistic effect of administering rituximab during CVP therapy" (Pet. 26) is directly contradicted by the black-letter rule that written description does not

require "*in haec verba* support for the claimed subject matter at issue." *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000); Dec. 9-11.

2. Petitioner Failed to Establish That the Challenged Claims Are Not Entitled to the Benefit of the '202 Application's Filing Date

Petitioner's arguments against priority boil down to piecemeal assertions that the claims do not find *in haec verba* support in the '202 Application. Pet. 22-27; *see*, *e.g.*, *id.* at 22. But as noted above, *supra*, §VII.B, this is not required.

Petitioner's lead argument focuses on a list of chemotherapeutic regimens on page 6 of the '202. Pet. 23. But page 6 identifies a *non-exclusive* group of therapies from which the "chemotherap[eutic] regimen ***may*** be selected." EX1034, 009. POSITA would have understood the inventor to be in possession of CVP as a chemotherapeutic regimen for use as part of the invention. "[T]he patent specification is written for a [POSITA], and such a person comes to the patent with the knowledge of what has come before." *Falkner*, 448 F.3d and 1366. Here, Petitioner's expert acknowledges POSITA would "have understood that CVP was a 'standard chemotherapy' in August 1998." EX1002, ¶¶65, 85 ("CVP was a standard therapy for lymphoma"), 101, 108. Thus, Dr. Lossos testified POSITA would have understood methods "for treating B-cell lymphoma comprising administering to a patient a therapeutically effective amount of a chimeric anti-CD20 antibody before, during, or subsequent to a chemotherapeutic regimen"

included administering the antibody before, during, or subsequent to CVP, and that the inventor was in possession of those methods. EX1034, 009, 058.

Petitioner argues the inventor did possess embodiments using CVP—even though CVP is expressly mentioned in the '202 Application and was known to be a standard chemotherapy—because the page 6 passage states the chemotherapy "may be *selected from the group consisting of,* at the very least," a list in which CVP does not expressly appear. Pet. 23 (emphasis original). But Petitioner's argument ignores that the passage permissively states the chemotherapy "***may***" be selected from the listed examples and introduces the list as including "***at the very least***" those examples. Petitioner cites no caselaw for the proposition that "consisting of" is so limiting in the written disclosure. Here, by its express language the page 6 list is *not* exhaustive.

The '202 Application further makes clear the page 6 list is not exhaustive by describing additional chemotherapeutic regimens (in addition to CVP) with an anti-CD20 antibody elsewhere in the '202 Application, even though (like CVP) they are not included in the page 6 list. *See* EX1034, 009, 032. The Board should reject Petitioner's attempt to elevate one portion of the specification that it prefers and to ignore the remainder. *See In re Skvorecz*, 580 F.3d 1262, 1270 (Fed. Cir. 2009); *In re Wright*, 866 F.2d 422, 425 (Fed. Cir. 1989).

Petitioner also argues the '202 merely renders obvious treating LG/F-NHL with R-CVP. But this subject matter is expressly disclosed. As discussed above, the express disclosure appears as a description of an arm of a clinical study of rituximab and CVP, which administered the rituximab before, during, or subsequent to the CVP. Here, it was the latter of those options. But that does not make the '202 Application any less a disclosure of treating LG/F-NHL by administering rituximab before, during or subsequent to CVP.

C. The Limitations Added in Claims 5-6 Are Entitled to the Benefit of the '202 Application

As explained above, the difference between claims 2 and 3, and claims 5 and 6, respectively, is that claims 5 and 6 require eight cycles of therapy with 375 mg/m^2 of R-CVP, spaced three weeks apart. *See*, *e.g.*, Pet. 28-30; Dec. 11-12. In light of the '202 Application's numerous examples supporting the 375 mg/m^2 dosage (*e.g.*, EX1034, 022, 025-028, 032-034, 038-039, 044; Dec. 10), the Petition's only remaining dispute is disclosure of the "once every 3 weeks for 8 doses" limitation in connection with CVP. Pet. 28-29; Dec. 11.

But in addition to disclosing "CVP as a chemotherapeutic regimen used in combination with rituximab (375 mg/m^2) to treat low-grade NHL" (*see* Dec. 10), the '202 Application explicitly discloses treatment schedules, including administering rituximab on day one of 21-day chemotherapy cycles—*i.e.*, once

every 3 weeks. In one example involving CHOP, the application discloses "Rituximab® [] administered on Day 1 and CHOP [] given on Days 1-3 every 21 days for 6 cycles"—and thus, with six cycles of CHOP in this example, administering rituximab on day one of each 21-day cycle meant every 3 weeks for six doses. EX1034, 040. But beyond this example, the application also expressly disclosed treating LG/F-NHL with rituximab (375 mg/m^2) in combination with "standard CVP therapy." EX1034, 032; Dec. 10; Pet. 25-26. And following institution, Petitioner's own expert correctly admitted "standard CVP therapy" was understood in 1999 to be six to eight cycles of CVP spaced three weeks apart. EX2027, 10:16-13:10[25]; see also EX2029, ¶40. Thus, POSITA reading the '202 Application would have understood the inventor, in referring to "standard CVP therapy," had possession of at least two CVP dosing regimens for use with rituximab:[26] (1) a regimen of eight cycles every three weeks (as in claims 5 and 6)

---

[25] At institution, the Board did not have the benefit of this admission. *Cf*. Dec. 12 (discussing, instead, Dr. Lossos' opening "opinion regarding dosing regimens that would have been *obvious*").

[26] As the Board correctly concluded (Dec. 10-11), and Petitioner conceded (Pet. 22), the '202 Application disclosed treatment with rituximab before, during and subsequent to chemotherapeutic regimens. *E.g.*, EX1034, 058. In addition to

on the high end of the range and (2) a regimen of six cycles every three weeks on the low end. *See, e.g.*, EX2024, 002; EX2029, ¶40; *Falkner*, 448 F.3d at 1364-65 (affirming Board's finding of adequate written description where application generally described claimed genus and several subgenus including subgenus claimed, even though application neither described nor incorporated by reference a description of the claimed subgenus that was known in the art; "A patent need not teach, and preferably omits, what is well known in the art."); *Bd. of Trs. of the Leland Stanford Junior Univ. v. Chinese Univ. of H.K.*, 860 F.3d 1367, 1375-78 (Fed. Cir. 2017) (Board was required to interpret what specification's reference to "products offered by Illumina" meant "*at the time of the invention*," and erred in failing to consider that this statement may have disclosed two alternatives (internal citations and quotations omitted, alterations original)); EX2029, ¶40. Accordingly, as Dr. Lossos' testimony confirms, POSITA would have recognized this disclosure of rituximab with "standard CVP therapy" supported the claimed requirement of eight cycles of therapy spaced three weeks apart. Claims 5 and 6 are entitled to their August 1999 priority date.

6-dose administrations (EX1034, 032), the '202 elsewhere described 8-dose administrations of rituximab to treat LG/F-NHL. EX1034, 022.

VIII. SECONDARY CONSIDERATIONS

Objective evidence of nonobviousness—such as the unexpected beneficial results achieved by the ’821 with a long-term outcomes, including median Time To disease Progression (“TTP”) and, relatedly, Progression-Free Survival (“PFS”), in LG/F-NHL patients using R-CVP—*must* be considered in any obviousness analysis. *See, e.g., Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966) (such objective indicia, referred to as “secondary considerations,” “give light to the circumstances surrounding the origin of the subject matter sought to be patented.”); *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (“Objective indicia … play a critical role in the obviousness analysis.”). This *mandatory* consideration is required to avoid precisely the sort of improper hindsight Petitioner employed here, distorting the art and isolating snippets from multiple references to try to piece together the ’821’s invention like a ransom note (some 18 years later). These material facts are “not just a cumulative or confirmatory part of the obviousness calculus but constitute[] independent evidence of nonobviousness…[that] enable[] the court to avert the trap of hindsight.” *Leo Pharm.*, 726 F.3d at 1358 (citations omitted). When present, such “objective evidence *must be ‘considered* as part of all the evidence, not just when the decision maker remains in doubt after reviewing the art.’” *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012).

Although Petitioner ignored secondary indicia, it was certainly aware of them—including the claimed invention's success at "lessen[ing] the likelihood or frequency of relapse" and increasing time to progression, as set forth in the patent itself (*e.g.*, EX1001, 2:8-9) and its file history (*attached by Petitioner* at EX1069, 120-21 (specifically discussing "Unexpected Results")). Petitioner was also aware that, as detailed above, the prior art gave no indication R-CVP would yield the surprisingly effective results it did. *Id*.; *cf. Merial Ltd. v. Virbac*, IPR2014-01279, Pap. 13, 26-27 (Jan. 22, 2015) (denying institution for, *inter alia*, failure to address known evidence of unexpected results). And although the Board warned it is "unfair to impose on [PO] in the first instance the burden of establishing unexpected results in a trial" when Petitioner knew of those results (*id.* at 26–27), PO is now forced to address these considerations before Petitioner has fulfilled its obligation to do so.

As detailed above, the '821 is directed to methods for treating LG/F-NHL comprising administering R-CVP (*see, e.g.*, claims 1-3, 5-6), and discloses this achieves, *inter alia*, a "beneficial synergistic effect in the patient" (*see, e.g.*, claim 1). As both the intrinsic record and *Petitioner's own assertions in this proceeding* make clear (*e.g.*, Pet. 17; Pap.14 (Rehearing Request), 3-8), the surprising benefits of this therapy include a vast improvement in median TTP ("the interval between randomization and progression, relapse after response, or death from any cause";

Ex. 1005, 004), reported, *e.g.*, to increase from 15 months (with CVP alone) to at least 32 months when patients were treated with the claimed method using 375 mg/m^2 of rituximab during CVP therapy. *See, e.g.*, EX1069, 120-21.

The surprising benefits also included unexpected results measured by survival—in particular, progression-free survival ("PFS"), reported in rituximab's current prescribing information as increasing from 1.4 years (with CVP alone) to 2.4 years with R-CVP. EX2015, 24 & Table 5. In this study, 322 patients with follicular NHL were randomized to receive up to eight 3-week cycles of CVP alone or in combination with 375 mg/m^2 rituximab on day one of each chemotherapy cycle (R-CVP). The main outcome measure of the study was PFS, defined as the time from randomization to the first of progression, relapse, or death. *Id*.

Moreover, these benefits were certainly unexpected. Prior to the '821, the benefits of R-CVP for LG/F-NHL treatment were not expected by POSITA: to the contrary, as detailed in §V.B.2, at the time of the '821 it was understood by those in the art that *doxorubicin* produced a particular beneficial effect with rituximab. Accordingly, doxorubicin-containing regimens—including the CHOP in Czuczman's R-CHOP regimen (EX1011), but *not CVP*—were believed likely to achieve a state of minimal tumor burden for which immunotherapy was thought to be most effective. *See supra* §II.B; EX1069, 120 (noting "the art at the time of

filing would have taught away from removing the doxorubicin from the C**H**OP chemotherapy regimen" to yield CVP) (emphases original); EX2029, ¶58. Thus, the benefits of the claimed R-CVP combination were surprising—providing independent evidence of nonobviousness, *Leo Pharm.*, 726 F.3d at 1358, and yet another reason the Board should deny the Petition's instituted obviousness challenges. *See, e.g.*, *Millenium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1369 (Fed. Cir. 2017) (reversing invalidity determination; "unexpected properties" of new compound and "ensuing pharmaceutical efficacy and benefit, negate the district court's ruling of obviousness").

IX. CONCLUSION

For the reasons above, PO requests that the Board confirm the Challenged Claims' patentability.

Respectfully submitted by: Dated: February 7, 2018

/J. Steven Baughman/
J. Steven Baughman (Reg. No. 47,414)

CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. §42.107 complies with the type-volume limitation in 37 C.F.R. §42.24(c)(1). According to the word-processing system's word count, the brief contains 13,957 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a)(1).

Dated: February 7, 2018

Respectfully Submitted,

By: /*Megan Raymond*/

Megan Raymond (Reg. No. 72,997)
Paul, Weiss, Rifkind, Wharton & Garrison LLP
2001 K St. NW
Washington, DC 20006
Tel: (202) 223-7300
Fax: (202) 403-3777
mraymond@paulweiss.com

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PATENT OWNER'S RESPONSE UNDER 37 C.F.R. §42.107 has been served in its entirety by causing the aforementioned document to be electronically mailed to the following attorneys of record for the Petitioner listed below:

Petitioner's Counsel of Record:

Michelle S. Rhyu (41,268)
Lauren J. Krickl (70,261)
James Brogan (35,833)
Eamonn Gardner (63,322)
Daniel Knauss (56,393)
Cooley LLP
Attn: Patent Group
1229 Pennsylvania Ave., NW, Suite 700
Washington DC, 20004
zCelltrion-PTAB-IPR@cooley.com

Dated: February 7, 2018

Respectfully Submitted,

By: */Megan Raymond/*
Megan Raymond (Reg. No. 72,997)
Paul, Weiss, Rifkind, Wharton & Garrison LLP
2001 K St. NW
Washington, DC 20006
Tel: (202) 223-7300
Fax: (202) 403-3777
mraymond@paulweiss.com