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Paper 60
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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 B2

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

FRANKLIN, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Celltrion, Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–6 of U.S. Patent No. 9,296,821 B2 (Ex. 1001, "the '821 patent"). Paper 2 ("Pet."). Biogen, Inc. ("Patent Owner") filed a Patent Owner's Preliminary Response to the Petition. Paper 10 ("Prelim. Resp.").

On October 6, 2017, we instituted an *inter partes* review of claims 1–3, 5, and 6. Paper 12 ("Dec. Inst.").[1] On February 7, 2018, Patent Owner filed a Patent Owner Response to the Petition. Paper 30 ("PO Resp.").

On April 30, 2018, in view of *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348 (2018), and Office Guidance on the Impact of *SAS* on AIA Trial Proceedings,[2] we modified our institution decision to include claim 4 and all grounds presented in the Petition. Paper 39. Upon doing so, we authorized Patent Owner to file a Supplemental Patent Owner Response to address the newly instituted claim and grounds, we authorized Petitioner to file a Reply to address both the Patent Owner Response and the Supplemental Patent Owner Response, and we modified the Scheduling Order accordingly. Papers 40–42. On June 6, 2018, Patent Owner filed a Supplemental Patent Owner Response. Paper 46 ("Supp. PO Resp."). On July 5, 2018, Petitioner filed a Reply to both Patent Owner Responses. Paper 47 ("Reply").

Thereafter, in response to Patent Owner's request, we authorized Patent Owner to file a submission identifying specific arguments and

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[1] Petitioner filed a Request for Rehearing regarding the denial of *inter partes* review of claim 4. Paper 14. The request was denied. Paper 25.
[2] https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial.

evidence in Petitioner's Reply that Patent Owner asserts are beyond the proper scope of the Reply, along with a short substantive response for each identified matter. Ex. 3001 (Board e-mail authorizing supplemental filings). At the same time, we authorized Petitioner to respond to Patent Owner's filing. *Id.* Patent Owner and Petitioner subsequently filed those authorized submissions. Papers 52 and 54. The parties have not filed any motions to exclude evidence. Patent Owner has not filed a motion to amend.

On August 15, 2018, the parties presented arguments at an oral hearing. The hearing transcript has been entered in the record. Paper 59 ("Tr.").

We issue this Final Written Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Having considered the record before us, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–6 of the '821 patent are unpatentable. *See* 35 U.S.C. § 316(e).

A. Related Proceedings

Petitioner and Patent Owner explain that they are not aware of any other pending proceedings involving the '821 patent. Pet. 4; Paper 6, 2. Petitions for *inter parties* review of claims in related U.S. Patent Nos. 8,329,172 B2 (IPR2017-01093) and 8,557,244 B1 (IPR2017-01094), filed by Petitioner along with the Petition for this proceeding were denied. IPR2017-01093, Paper 12 (Denying Institution); IPR2017-01094, Paper 12 (Denying Institution) and Paper 15 (Denying Rehearing Request).

B. The '821 Patent

The '821 patent relates to methods of treating B-cell lymphomas, including low grade or follicular non-Hodgkin's lymphoma ("NHL"), by administering chimeric anti-CD20 antibodies in combination with

chemotherapy, *e.g.*, CVP (cyclophosphamide, vincristine, and prednisone).. Ex. 1001, 2:21–31, 4:24–26, 23:60–67 (claim 1). A "preferred chimeric [anti-CD20] antibody is C2B8 (IDEC Pharmaceuticals, Rituximab)." *Id.* at 3:3–5. According to the Specification, "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." *Id.* at 2:24–28.

C. Illustrative Claims

Each challenged claim is an independent claim. Claims 1 and 4 are reproduced below:

> 1. A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL) comprising administering to a patient a therapeutically effective amount of rituximab during a chemotherapeutic regimen, wherein the chemotherapeutic regimen consists of cyclophosphamide, vincristine, and prednisone (CVP therapy), wherein the method comprises administering 375 mg/m^2 of rituximab, and wherein the method provides a beneficial synergistic effect in the patient.
>
> 4. A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL) comprising administering to a patient a therapeutically effective amount of rituximab during a chemotherapeutic regimen, wherein the chemotherapeutic regimen consists of cyclophosphamide, vincristine, and prednisone (CVP therapy), wherein the method comprises administering 375 mg/m^2 of rituximab once every 3 weeks for 8 doses, and wherein the method provides a beneficial synergistic effect in the patient.

D. The Instituted Grounds of Unpatentability

Petitioner challenges the patentability of the claims as follows:

Claims	Basis	References
1–6	Pre-AIA § 102	Marcus[3]
3 and 6	Pre-AIA § 103	Marcus and the '137 Patent[4]
1–3	Pre-AIA § 103	Czuczman,[5] IDEC 10-K/A,[6] Foon,[7] and Dana[8]
4–6	Pre-AIA § 103	Czuczman, IDEC 10-K/A, Foon, Dana, Link,[9] and Piro[10]
3 and 6	Pre-AIA § 103	Czuczman, IDEC 10-K/A, Foon, Dana, Link, Piro, and the '137 Patent

[3] Marcus et al., *CVP chemotherapy plus rituximab compare with CVP as first-line treatment for advanced follicular lymphoma*, 105 BLOOD 1417–23 (2005) (Ex. 1005).
[4] U.S. Patent 5,736,137 issued to Anderson et al. on Apr. 7, 1998. (Ex. 1007).
[5] Czuczman et al., *IDEC-C2B8 and CHOP Chemoimmunotherapy of Low-Grade Lymphoma*, 86 BLOOD 10 Supp. 1:55a (Abstract 206) (1995) (Ex. 1011).
[6] IDEC Pharmaceuticals Corp., Form 10-K/A Annual Report for the Fiscal Year Ended Dec. 31, 1997, filed with the U.S. Securities and Exchange Comm. (Ex. 1006).
[7] Foon et al., Chapter 111: *Lymphomas*, Williams Hematology, 5th Ed. 1076–96 (1990) (Ex. 1008).
[8] Dana et al., *Long-Term Follow-Up of Patients with Low-Grade Malignant Lymphomas Treated with Doxorubicin-Based Chemotherapy or Chemoimmnotherapy*, 11 J. CLIN. ONCOL. 644–51 (1993) (Ex. 1009).
[9] Link et al., *Phase II Pilot Study of the Safety and Efficacy of Rituximab in Combination with CHOP Chemotherapy in Patients with Previously Untreated Intermediate- or High-Grade NHL, Program/Proceedings*, 17 AM. SOC. CLIN. ONCOL. 3a (Abstract 7) (1998) (Ex. 1010).
[10] Piro et al., *RITUXAN™ (rituximab, IDEC-C2B8): Interim analysis of a phase II study of once weekly times 8 dosing in patients with relapsed low-grade or follicular non-Hodgkin's lymphoma*, 90 BLOOD 10 Supp. 1:510a (Abstract 2272) (1997) (Ex. 1004).

Petitioner also relies upon the Declarations of Izidore Lossos, M.D. (Ex. 1002) and Walter Longo, M.D. (Ex. 1003). Patent Owner relies upon the Declaration of Peter McLaughlin, M.D. (Ex. 2029).

II. ANALYSIS

A. Claim Construction

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

"beneficial synergistic effect"

Petitioner and Patent Owner propose constructions for the claim phrase "beneficial synergistic effect," recited by claims 1 and 4. Pet. 30–31; PO Resp. 13–17. Petitioner asserts in the Petition that the broadest reasonable construction of the claim phrase is "an improvement in clinical outcome." Pet. 31. Petitioner supports that proposed construction by referring to (a) the Specification description that "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," Ex. 1001, 2:24–28,[11] and (b) a description in Applicant's Supplemental Information Disclosure Statement that "[p]atients treated with R-CVP experienced median progression free survival (PFS) of 2.4 years compared with 1.4 years in patients treated with CVP only, demonstrating a beneficial synergistic effect in the patient." Ex. 1069, 120.[12]

Patent Owner asserts that Petitioner's proposed construction reads "synergistic" out of the claim phrase. PO Resp. 14–16. Patent Owner asserts that either the Board's construction in the Institution Decision, i.e., "a clinical outcome resulting from combination therapy that reflects a greater beneficial effect than the additive effects of the uncombined therapies when administered alone," Dec. Inst. 7, or Patent Owner's initially proposed construction, i.e., "an effect better than the additive effects of rituximab and CVP administered alone" is proper, PO Resp. 13–14. Patent Owner supports those constructions by referring to the Specification description of the term "synergistic" as meaning a therapeutic combination producing an effect "better than the additive effects of either therapy administered alone." PO Resp. 14 (citing Ex. 1001, 3:44–47).

Patent Owner also refers to Applicant's discussion of the term "synergistic" during the prosecution of Application No. 11/840,956, the

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[11] We join the parties in citing to the page numbering added to exhibits by the filing party, rather than the original page numbering therein, with an exception for the '821 patent (Ex. 1001).
[12] File history of the '821 patent (Application No. 13/524,896) (Ex. 1069).

parent application to the '821 patent. *Id*. (citing Ex. 2006, 14–15).[13] According to Patent Owner, "applicant similarly equated more-than-additive results with 'synergistic.'" *Id*. For example, Patent Owner refers to Applicant's description of data from the study disclosed in Marcus as demonstrating that "[t]he complete responses (CRs) and extended median TTP achieved with the presently claimed combination [R-CVP] were more than additive, *i.e*., they were synergistic results." *Id*. at 14–15 (quoting Ex. 2006, 14–15). Patent Owner notes that "Applicant cited to this same data during the '821's prosecution" as evidence that the claimed methods provide a beneficial synergistic effect. *Id*. (citing Ex. 1069, 121 and 137).

In the Reply, Petitioner asserts that requiring "beneficial synergistic effect" to involve a "greater beneficial effect than the additive effects of the uncombined therapies" is not the broadest reasonable interpretation of the term as it, allegedly, "contradicts a POSA's understanding of the term, as PO's expert testified." Pet. Reply 6. According to Petitioner, Patent Owner's declarant, Dr. McLaughlin, "testified that a POSA would have found the Board's construction too 'stringent'" because the term "'synergy' in the field lacked 'rigidity' and often included 'sensitization' or 'potentiation' of the effects of one treatment by another – consistent with the construction proposed by the Petitioner: 'an improvement in clinical outcome.'" *Id*. at 7 (quoting Ex. 2030, 49:22–50:8, 80:1–10). Petitioner asserts that Dr. McLaughlin agreed that "sensitization means that you're

[13] Amendment and Reply under 35 C.F.R. § 1.111, filed Aug. 25, 2010, in Application No. 11/840,956 (Ex. 2006).

potentiating the activity of a compound that has an activity." *Id*. (quoting Ex. 2030, 81:14–19).

Petitioner asserts that the description of "better than additive" effects in the Specification and prosecution history "need not be limiting in light of PO's other uses of 'synergy.'" Pet. Reply. 7. According to Petitioner, in the prosecution history, Applicant did not rely only any "better-than-additive effect" when referring to an improvement in clinical outcome as meeting the definition of synergistic effect. *Id*. at 7–8. In particular, Petitioner refers to Applicant's statement that "patients treated with R-CVP experienced median progression free survival (PFS) of 24 years compared with 1.4 years in patients treated with CVP only, demonstrating a beneficial synergistic effect in the patient." *Id*. at 8 (quoting Ex. 1069, 120). As for the Specification, Petitioner asserts that the disclosure includes a reference to "the results in Demidem 1997 (Ex. 1079), which describe rituximab-based sensitization of cells to chemotherapy, as an example of 'synergy.'" *Id*. (citing Ex. 1001, 12:57–59). According to Petitioner, the broadest reasonable interpretation of "beneficial synergistic effect," slightly altered from its initial proposed meaning of "an improvement in clinical outcome," *see* Pet. 31, should be "an improvement in efficacy compared to one therapy alone," Pet. Reply 8.

The Specification summarizes the invention, in part, by stating, "[i]n particular, 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." Ex. 1001, 2:24–28 (emphasis added). Thereafter, when discussing the combination of anti-CD20 antibody (rituximab) and a cytokine, the Specification provides a description of such synergistic effect, as follows:

> The combined therapies of the present invention include a method for treating B-cell lymphoma comprising administering at least one chimeric anti-CD20 antibody and at least one cytokine. In particular, the invention includes a method for treating B-cell lymphoma comprising *administering a synergistic therapeutic combination* comprising at least one anti-CD20 antibody and at least one cytokine, *wherein the therapeutic effect is better than the additive effects of either therapy administered alone*.

Id. at 3:39–48 (emphasis added). According to the Specification the combination therapy is deemed synergistic when "the therapeutic effect is better than the additive effects of either therapy administered alone." *Id*. at 3:45–47. Based on the above disclosures, we find that the Specification sets forth with reasonable clarity and deliberateness the meaning of a "synergistic effect" in the context of administering rituximab in combination with another therapeutic compound of the invention, i.e., cytokines, radiotherapy, myeloablative therapy, or chemotherapy. Moreover, Patent Owner has shown persuasively that Applicant's discussion during the prosecution of the '821 Application explaining how the data disclosed in Marcus demonstrates a "beneficial synergistic effect" is consistent with the Specification description. Accordingly, based upon the Specification definition of the term "synergistic effect, we interpret the claim phrase "beneficial synergistic effect" as meaning "a therapeutic effect resulting from combination therapy that reflects a greater beneficial effect than the additive effects of either therapy when administered alone."

In the Reply, Petitioner acknowledges the Specification description of "synergistic effect" as requiring "better than the additive effects of either therapy administered alone," but contends that other uses of "synergy" in the

Specification and prosecution history demonstrate the construction need not be so limiting. Pet. Reply 8. In support of that contention, Petitioner again relies upon a reference in the Specification to Demidem 1997. *Id*. According to Petitioner, Demidem 1997 provides a broader description of "synergy" by referring to "rituximab-based sensitization of cells to chemotherapy, as an example of 'synergy.'" *Id*. (citing Ex. 1001, 12:57–59, 19:5–9; Ex. 1079).

Demidem 1997 describes an "*in vitro* study examin[ing] the sensitizing effect of C2B8 antibody [rituximab] on the DHL-4B lymphoma line to various cytotoxic agents." Ex. 1097, Abstract. Demidem 1997 explains that the findings of the study "demonstrate that C2B8 antibody potentiates the sensitivity of DHL-4 tumor cells to several cytotoxic agents." *Id*. The reference expressly refers to "synergy" when describing previous studies demonstrating "that combination treatments of cytokines/antibody and chemotherapeutic drugs *result in potentiation of tumor cells sensitivity, reversal of drug resistance and synergy achieved* with subtoxic concentration of cytotoxic agents." *Id*. at 3 and 9 (emphasis added).

The Specification refers to Demidem 1997 when describing a Phase II trial initiated to evaluate the combination of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and Rituximab to treat low-grade or follicular NHL "because their mechanisms of action are not cross-resistant, and Rituximab is synergistic with certain cytotoxic drugs, including doxorubicin." Ex. 1001, 12:53–58 (citing Ex. 1079).

Dr. McLaughlin's testimony, relied upon by Petitioner for this issue, states that he has "use[d] the word 'synergy' with a looser definition than the board's" in one of his publications referring to Demidem 1997. Ex. 2030,

79:12–80:10. Dr. McLaughlin explains that he used the term as meaning "sensitization," and further explained that his use of the term "synergy" may have been done so "ill-advisedly," while noting that he thinks "there wasn't rigidity about the use of that word," and ultimately deciding "[s]ensitization would have been the better choice." *Id*. at 80:24–81:5. Dr. McLaughlin agreed that "other people in the field used synergy when they meant sensitization," and that "for better or worse, those words were used interchangeably." *Id*. at 81:8–13.

Thus, according to Petitioner, Demidem 1997's discussion of sensitization, potentiation, and synergy, along with Dr. McLaughlin's recognition of his loose use of those terms, demonstrates that the Specification description of "synergistic effect" as involving "greater than the additive effects of either therapy when administered alone" is non-limiting. We disagree. Rather, we view Petitioner's evidence as demonstrating that those of skill in the art would have understood that potentiating tumor cells sensitivity to a compound may broadly, or loosely be considered synergy, in a general sense. However, with respect to the claimed invention, the Specification expressly sets forth specific requirements for demonstrating a beneficial synergistic effect in, as Dr. Laughlin describes, a more stringent manner.[14] Even so, Demidem 1997

[14] We note that, contrary to Petitioner's assertion, Dr. McLaughlin did not provide testimony that our initial interpretation of the claim phrase "beneficial synergistic effect" was "too stringent," in view of the Specification description for that claim phrase. *See, e.g.*, Ex. 2030, 49:22–50:8, 79:13–81:13. Rather, his testimony reveals that he views our interpretation to be more precise than his usage in other publications. *See, e.g.*, *id*. at 80:24–81:13.

describes "potentiation of tumor cells sensitivity, reversal of drug resistance and synergy achieved" resulting from combination therapies. Ex. 1079, 3 and 9. Whether or not potentiation and sensitization achieves a "synergistic effect" as defined by the Specification, i.e., "greater than the additive effects of either therapy when administered alone," in every instance, we find that the Specification recognizes Demidem 1997's report of "sensitiz[ing] the cells to the cytotoxic effect of various agents resulting in significant potentiation of tumor cell killing" as one such instance that meets the Specification description of synergistic effect. Ex. 1001, 12:56–58. As a result, we find that the use of the term "synergistic" in the Specification when referring to Demidem 1997 does not refer to a different or broader meaning for the claim phrase "beneficial synergistic effect" than what is set forth in the Specification description of "synergistic effect." Rather, we view the reference to Demidem 1997 as a reference to a specific example of such synergistic effect, achieved via sensitization and potentiation of the studied cell line.

Petitioner's reference to Applicant's use of the term "synergy" in the prosecution history does not persuade us to change our finding. Petitioner asserts that Applicant relies upon a broader interpretation of "beneficial synergistic effect by stating that "patients treated with R-CVP experienced median progression free survival (PFS) of 24 years compared with 1.4 years in patients treated with CVP only, demonstrating a beneficial synergistic effect in the patient." *Id*. at 8 (quoting Ex. 1069, 120). Although the portion of Applicant's Response to Office Action during the prosecution of the '896 application quoted by Petitioner does not include details regarding the effect of rituximab alone on PFS, the discussion that follows states that

"[a]dditional data obtained in accordance with the presently claimed invention is provided by Marcus," along with a table summarizing "certain therapeutic results achieved with rituximab alone, CVP alone, or the presently claimed combination," i.e., R-CVP. *Id*. That comparative data reveals that the Median Time to Progression ("MTP") and the percentage of patients achieving Complete Response ("CR") with an R-CVP treatment regimen was better than the additive effects of treatment with rituximab alone or CVP alone. *Id*. at 121. Thus, unlike with Applicant's response regarding PFS, Applicant's response regarding MTP and CR provide sufficient detail to demonstrate how the R-CVP combination achieves a beneficial synergistic effect in a manner prescribed by the Specification.

We determine that construction of additional claim terms is not necessary for purpose of this Decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (only terms that are in controversy need to be construed, and only to the extent necessary to resolve the controversy).

B. Level of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

According to Petitioner, a person of ordinary skill in the art at the time of the invention would have been "a practicing physician specializing in hematology or oncology, with at least three years of experience in treating patients with NHL." Pet. 31–32 (citing Ex. 1002 ¶ 24). Patent Owner does

not address Petitioner's position on this matter and does not propose its own description for a person of ordinary skill in the art at the time of the invention.

Based on the record as a whole, we determine that Petitioner's description sufficiently characterizes the level of ordinary skill in the art relevant to the claimed invention. Moreover, after reviewing the credentials of Drs. Lossos and McLaughlin, we consider each of them to be qualified to provide an opinion on the knowledge of a person of ordinary skill in the art at the time of the invention.[15] We also note that the applied prior art reflects the appropriate level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). The relative weight that we assign such testimony, however, is subject to additional factors. *See, e.g.*, Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,763 (Aug. 14, 2012) ("Opinions expressed without disclosing the underlying facts or data may be given little or no weight.").

C. The '821 Patent Priority Date

The '821 patent issued from U.S. Application No. 13/524,896 ("the '896 application") filed on June 15, 2012. Exs. 1001 and 1069. The '896 application is a divisional of U.S. Application No. 11/840,956, which is a continuation of U.S. Application No. 10/196,732, which is in turn a continuation of U.S. Application No. 09/372,202 ("the '202 application") filed on August 11, 1999. Exs. 1001 and 1034, 1 (the '202 application file

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[15] Petitioner does not rely on Dr. Longo's testimony (Ex. 1003) to support its unpatentability contentions. *See, e.g.*, Pet. 17 (referring to Ex. 1003 as support for the public availability of the E1496 Protocol and Consent Form-a reference not included in any unpatentability ground).

history indicating a corrected filing date of August 11, 1999, for the '202 application).

Petitioner asserts that none of the claims of the '821 patent are entitled to a priority date earlier than June 15, 2012, because each of those claims lacks written description support in the specification of the '202 application. Pet. 18–30. Patent Owner disagrees, asserting that the disclosures of the '202 application demonstrate that the inventor had possession of the inventions set forth in the claims of the '821 patent. *See* PO Resp. 56–64.[16] For the reasons that follow, based on the record as a whole, we determine that Petitioner has shown persuasively that claims 4–6 are not supported by the disclosures of the '202 application. As for claims 1–3, we agree with Patent Owner that the evidence of record demonstrates that the '202 application provides written description support for those claims.

"Patent claims are awarded priority on a claim-by-claim basis based on the disclosure in the priority applications." *Lucent Technologies, Inc. v. Gateway, Inc.*, 543 F.3d 710, 718 (Fed. Cir. 2008). To receive the benefit of a previous application, *every feature* recited in a particular claim at issue must be described in the prior application. *See In re Van Langenhoven*, 458 F.2d 132, 137 (CCPA 1972) ("The fact that *some* of the elements of the breech claims have the support of the parent and foreign applications does not change the result. *As to given claimed subject matter, only one effective*

[16] Patent Owner does not assert priority based upon the filing date of the provisional or intervening applications. *See* PO Resp. 56–64. Thus, we consider the issue of priority with respect to the '202 application only.

date is applicable." (emphases added)); *accord In re Chu*, 66 F.3d 292, 297 (Fed. Cir. 1995).

As the Federal Circuit has noted, however, "[i]n order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *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). Rather, "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 Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

Regarding claims 1–3, Petitioner asserts that "[t]he '202 application does not describe the combination of administering rituximab *during CVP* chemotherapy to treat low-grade or follicular lymphoma, where the method provides a beneficial synergistic effect." Pet. 20–21. Petitioner recognizes the '202 application "mention[s] the words in the recited elements," however, Petitioner contends that the disclosures "do[] not describe combining these elements to achieve the claims methods of treatment." *Id*. at 21–22, 26–27. According to Petitioner, "the cited elements are dispersed throughout the specification" without conveying that Applicant had "possession of the combination of (1) a method of treating low grade NHL; (2) comprising administering anti-CD20 antibody during CVP chemotherapy; (3) to achieve a beneficial synergistic effect." *Id*. at 22 (citing Ex. 1002 ¶ 80.), *see also* PO Reply 4–5. We note that third element is required by claim 1, but not claims 2 and 3. *See* Ex. 1001, 23:60–24:67.

We view Petitioner's argument as requiring the '202 application to provide *in haec verba* support for the claimed subject matter. Such argument

is not well taken. *See Purdue Pharma*, 230 F.3d at 1323; *see also Ariad*, 598 F.3d at 1352 (written description need not be in any particular form or an *in haec verba* recitation of the claimed invention). When considered under the proper written description standard, we determine that the undisputed disclosures in the '202 application would have reasonably conveyed to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.

In particular, Petitioner acknowledges the following disclosures in the '202 application: (a) original claim 17 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," Pet. 22 (quoting Ex. 1034, 58); (b) 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, *id*. at 23 (citing Ex. 1034, 61); (c) CVP is disclosed as a chemotherapeutic regimen administered prior to rituximab maintenance therapy ("375 mg/m^2 weekly times 4 every 6 months") to treat low-grade NHL, *id*. at 25–26 (citing Ex. 1034, 32), and (d) that "treatment with anti-CD20 antibody provides a beneficial synergistic effect when administered in combination with . . . chemotherapy," *id*. at 26 (quoting Ex. 1034, 6).

Based upon our review, a person of ordinary skill in the art would have considered those disclosures together and not as separate, unrelated descriptions. Disclosures (b) and (c) provide exemplary descriptions for certain method elements recited in disclosure (a), i.e., the B-cell lymphoma can be low grade NHL, the chemotherapeutic regimen can be CVP therapy, and the rituximab dose can be 375 mg/m^2. In terms of administering the

rituximab "during" a chemotherapeutic regimen, disclosure (a) expressly recites that option by describing administering rituximab "before, during or subsequent to" the chemotherapeutic regimen.

Moreover, disclosure (d) reasonably conveys to those of skill in the art that the inventors understood that such a method of combining chemotherapy and rituximab provides a beneficial synergistic effect. That description is not diminished because the disclosure "makes no specific reference to a beneficial, synergistic effect of administering rituximab *during CVP* therapy," as Petitioner asserts. Pet. 26. Indeed, when describing a beneficial synergistic effect resulting from treatment with rituximab in combination with chemotherapy, Ex. 1034, 6, the disclosure does not limit the type of chemotherapy that may be combined with rituximab to achieve the synergistic effect. Thus, we do not find that the disclosure would have conveyed to a skilled artisan that CVP would be excluded from such combination.

Based on the foregoing, we agree with Patent Owner that the '202 application provides written description support for each of claims 1–3. Accordingly, we determine that claims 1–3 are entitled to receive benefit of the '202 application filing date of August 11, 1999. As discussed below, this determination impacts our consideration of Petitioner's challenges of claims 1–3 based upon Marcus.

Regarding claims 4–6, Petitioner contends that the '202 application fails to describe administering rituximab "once every 3 weeks for 8 doses," as recited by those claims. Pet. 28–30; Ex. 1001, 25:13–15, 26:1–8. According to Petitioner, the application instead describes administering rituximab, as a single agent, *weekly* for eight doses. Pet. 29–30.

Patent Owner identifies a disclosure in the application for "administering rituximab on day one of 21-day chemotherapy cycles— i.e., once every 3 weeks." PO Resp. 64–65 (citing Ex. 1034, 40). Patent Owner does not identify any portion of the application that describes administering rituximab once every three weeks for *eight* doses in combination with chemotherapy. Rather, Patent Owner identifies specification descriptions of a dosing regimen involving administering rituximab with chemotherapy every three weeks for *six* cycles, i.e., doses. *Id*. at 65 (citing Ex. 1034, 26 and 32). Although "it is unnecessary to spell out every detail of the invention in the specification," satisfying the written description requirement still demands that enough detail "must be included to convince a person of skill in the art that the inventor possessed the invention." *Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006) (citation omitted).

Patent Owner asserts also that the application "expressly disclosed treating LG/F-NHL with rituximab (375 mg/m^2) in combination with 'standard CVP therapy.'" PO Resp. 65 (citing Ex. 1034, 32). Patent Owner draws support from the deposition testimony of Petitioner's declarant, Dr. Lossos, who agreed that "standard CVP therapy" was known to involve six to eight cycles of CVP spaced three weeks apart. *Id*. (citing Ex. 2027, 10:16–13:10; Ex. 2029 ¶ 40). According to Patent Owner, based on that knowledge, a person of ordinary skill in the art would have understood that, by referring to "standard CVP therapy," the inventor had possession of the claimed dosing regimen for rituximab once every three weeks for eight doses. *Id*.

We disagree with Patent Owner. The portion of the application referenced by Patent Owner as "expressly disclos[ing] treating LG/F-NHL

with rituximab (375 mg/m^2) in combination with 'standard CVP therapy'" describes a Phase II study wherein patients were administered standard CVP therapy first, and then those patients who responded to the CVP therapy received rituximab as a "maintenance therapy." Ex. 1034, 32. As discussed above, we recognize that disclosure, along with other descriptions in the application that rituximab may be administered "before, during or subsequent to" the chemotherapeutic regimen, convey that the inventors were in possession of administering rituximab during chemotherapy. However, regarding the *dosing schedule* of rituximab, the application expressly describes the rituximab maintenance therapy as "375 mg/m^2 *weekly times 4* every 6 months for 2 years (Arm C) or to observation (Arm D)." *Id*. Patent Owner has not directed us to any portion of the application describing or otherwise conveying to a skilled artisan that the inventors had possession of instead administering the rituximab using the asserted dosing schedule for CVP, i.e., once every three weeks for eight doses. In other words, Patent Owner has not identified application disclosure(s) describing the combination therapy as meaning administering each therapy in the combination according to the dosing schedule for standard CVP. At most, Patent Owner's argument suggests that administering the two therapies in the manner recited by claims 4–6 may have been an obvious modification of what the '202 application describes. *See* Ex. 1002 ¶ 118 (Dr. Lossos discussing obviousness of modified dosing schedule). However, such a showing is unavailing with respect to priority claims. *Lockwood v. American Airlines*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) ("One shows that one is 'in possession' of *the invention* by describing *the invention*, with all its claimed limitations, not that which makes it obvious.").

Based on the foregoing, we agree with Petitioner that the '202 application does not provide written description support for claims 4–6. Accordingly, we find that Petitioner has established that claims 4–6 are not entitled to receive benefit of the '202 application filing date of August 11, 1999. As a result, we recognize the June 15, 2012, filing date of the '896 Application as the earliest priority date for claims 4–6. As discussed below, this determination impacts our consideration of Petitioner's challenges of those claims based upon grounds including Marcus.

D. Public Accessibility of Marcus, Czuczman, Foon and Dana

Patent Owner asserts that the Petition "did not even attempt to show that Foon, Czuczman, Dana, or Marcus are prior art printed publications." PO Resp. 18. In particular, Patent Owner asserts that Petitioner asserted that Marcus, Czuczman, and Dana each came from journals without providing evidence to establish that the articles "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." *Id*. at 19. Patent Owner asserts also that Petitioner asserted a publication date for each article without explaining "how Petitioner came up with the asserted publication dates." *Id*. As for Foon, Patent Owner asserts that Petitioner similarly did not provide any "explanation or proof" that the reference was published and publicly available. *Id*.

The Federal Circuit has held that "public accessibility" is "the touchstone" in determining whether a reference is a printed publication. *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986). "A given reference is 'publicly accessible' upon a satisfactory showing that such document 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." *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)).

Based on the current record, we consider Patent Owner's arguments relating to the public accessibility of Marcus, Czuczman, Foon and Dana hollow. We note that Patent Owner does not assert or suggest that any of those references, which come from well-known journals or a well-known book, are not printed publications. Moreover, Petitioner has identified the source and publication date for each reference in the Petition. Pet. 32–34. Further, Marcus, Czuczman and Dana each contain information identifying the journal in which they were published, including the volume, number, and date of publication. Exs. 1005, 1011, and 1009. Similarly, Foon identifies the book, edition, part, and chapter in which it is published, along with the publication year. Ex. 1009. In other words, the public accessibility of these references is extent on their face.

Specifically, we make the following findings based upon the contents of each challenged exhibit. Marcus is an article appearing in volume 105, number 4 of "Blood," a journal of The American Society of Hematology. Ex. 1005, 1 and 3. The article contains a statement that it was "[p]republished online as Blood First Edition Paper, October 19, 2004, and subsequently published on February 15, 2005. *Id*. at 2–3. A stamped label appears on the journal cover in the exhibit indicating that it was "received" by "UC San Diego" on "02-16-05." *Id*. at 1. The exhibit additionally describes the multiple indexing and abstracting services for the journal. *Id*. at 2.

Czuczman is an abstract appearing in volume 86, number 10, and supplement 1 of the same "Blood" journal. Ex. 1011, 1. The exhibit contains a November 15, 1995 publication date. *Id*. A stamped label appears on the journal cover in the exhibit indicating that it was "received" by "UC San Diego" on "11-27-95." *Id*.

Dana is an article appearing in volume 11, number 4 of the "Journal of Clinical Oncology," the "Official Journal of the American Society of Clinical Oncology." Ex. 1009, 1. The article contains an April 1993 publication date and a statement that the journal is "published monthly." *Id*. at 1–2. A label notification appears on the journal cover in the exhibit indicating that it was "received" by "University of California Los Angeles" on "Apr 08 1993." *Id*. at 1.

Foon is a chapter appearing in the fifth edition of "Williams Hematology" textbook. Ex. 1008, 1. The exhibit contains Library of Congress "Cataloging-in-Publication Data," including a 1995 cataloging date. *Id*. at 3.

Based upon the foregoing findings, we determine that Petitioner has shown by a preponderance of the evidence that Marcus, Czuczman, and Dana are each printed publications, and that each reference was publicly accessible, at the latest,[17] on the date the publication was stamped as having been received by the university library. Thus, Marcus was publicly available at least by February 16, 2005, Czuczman was publicly available at least by

[17] We note that, in many cases, a party may establish that a journal article which is circulated and or catalogued in a routine manner may be presumed to have been publicly accessible on the publication date contained in the article.

November 27, 1995, and Dana was publicly available at least by April 8, 1993. Based on the foregoing, we also determine that Petitioner has shown by a preponderance of the evidence that Foon is a printed publication that was publicly accessible as of its 1995 cataloging date.

In the Reply, Petitioner reiterates that Marcus, Dana, and Czuczman each contain a library date-stamp. Pet. Reply 9. Petitioner also relies upon the Declaration of Dr. Hall-Ells, who holds a Ph.D. in Library Science and is a member of the Editorial Board for the "premier cataloging journal, Library Resources and Technical Services." Ex. 1303 ¶¶ 6–7. Dr. Hall-Ellis provides testimony regarding the handling of printed journal subscriptions among libraries, i.e., stamping the cover of each journal with the date it was received. *See, e.g.*, *id*. at 34. Based upon her review of the Marcus, Dana, and Czuczman exhibits, Dr. Hall-Ellis testified that each reference was publicly accessible no later than the date on the library received-by stamp appearing on the cover of the journal for each referenced article. *Id*. ¶¶ 44–61.

As for the textbook in which Foon is printed, Dr. Hall-Ellis explained how the catalog record included on the exhibit reveals that the book was cataloged at the Library of Congress for the National Library of Medicine ("DNLM/DLC") and that the record number (310764844) was created by a cataloger on August 16, 1994. Ex. 1303 ¶¶ 42–43. Based upon these and other aspects of her review of Exhibit 1008, Dr. Hall-Ellis determined that the exhibit was published and accessible to the public no later than August 16, 1994. *Id*. at 39–43.

Patent Owner asserts that "Petitioner's reliance on an entirely new expert declaration (EX1303) in an attempt to support the prior art status of

documents is improper." Paper 52, 1.[18] In support, Patent Owner cites two decisions without discussing or otherwise explaining their applicability or support for its contention. *Id*.

We are not persuaded by Patent Owner's contention. In the Reply, Petitioner explains that the Hall-Ellis declaration was submitted in response to Patent Owner's argument that Petitioner's evidence was insufficient to prove public availability. Paper 54, 1. Based upon our review of the Patent Owner Response, the Petitioner's Reply, and the Hall-Ellis declaration, we agree with Petitioner that the portion of the Reply addressing Patent Owner's arguments challenging Petitioner's evidence relating to the public accessibility of Marcus, Czuczman, Foon, and Dana, *see* Pet. Reply 9–10, along with the cited portions of the Hall-Ellis declaration in the Reply, are within the proper scope of a reply, as set forth in 37 C.F.R. 42.23(b), i.e., a "reply may only respond to arguments raised in the corresponding opposition or patent owner response".

Moreover, we find the testimony of Dr. Hall-Ellis to be credible and persuasive such that it provides additional support for our findings and conclusions regarding the printed publication status of Marcus, Czuczman, Foon, and Dana. In particular, Dr. Hall-Ellis explains persuasively that it was a customary practice for libraries having journal subscriptions to stamp the cover of each journal with the date it was received. Ex. 1303 ¶ 34. Further, Dr. Hall-Ellis explained that stamping the cover of each journal with the date it was received and that the journal would have been publicly

[18] Patent Owner has not filed a motion to strike or a motion to exclude relating to the Petitioner's Reply arguments or evidence regarding this issue.

accessible at the library as of that stamped date. *Id*. ¶¶ 44–61. Regarding the textbook containing Foon, Dr. Hall-Ellis provided credible testimony regarding the cataloguing codes contained in the book and explained that such codes reveal the date on which the book was cataloged at the Library of Congress for the National Library of Medicine ("DNLM/DLC") and that the book would have been publicly accessible on that date. *Id*. ¶¶ 42–61.

Accordingly, Marcus, Czuczman, Foon and Dana are printed publications. The status of these publications as prior art depends upon the priority date of the claim challenged, as discussed above in Section II. C. and further in the following analyses.

E. Anticipation by Marcus

Petitioner asserts that claims 1–6 are unpatentable as anticipated by Marcus. Pet. 38–44. Patent Owner disagrees. PO Supp. Resp. 18–19.

1. Marcus

Marcus is a journal article discussing a randomized trial comparing the effects of administering CVP chemotherapy alone and in combination with rituximab as a first-line treatment for advanced follicular lymphoma. Ex. 1005, Title. As background, Marcus discusses a Phase II trial of patients with relapsed/refractory indolent NHL who received 4 weekly infusions of rituximab (375 mg/m^2) for whom a response rate of 48% was obtained, with a median time to progression of 9 months. *Id*. at 3–4. Marcus explains that when the same rituximab regimen was given to previously untreated patients with follicular lymphoma in an early Phase II study, the response rate observed was 73% (no worse or better than what was obtained with chemotherapy). *Id*. at 4.

Additionally, Marcus describes data from *in vitro* studies as suggesting that "rituximab can sensitize lymphoma cell lines to chemotherapy" and that "a synergistic effect between rituximab and various cytotoxic agents has been demonstrated." *Id*. Marcus explains that in a phase 2 study of rituximab in combination with CHOP, patients with previously untreated and relapsed low-grade or follicular lymphoma achieved an overall response rate of 95%, with a 55% complete response rate. *Id*. Marcus explains that, in view of those results, its study seeks to evaluate "the addition of rituximab to a widely used standard chemotherapy regimen (CVP)" compared to CVP alone in previously untreated patients with follicular lymphoma. *Id*.

In Marcus' study, patients were treated with CVP every 21 days for a maximum of 8 cycles, wherein those receiving rituximab (375 mg/m^2) were additionally administered such drug on day 1 of each therapy cycle. *Id*. at 4. Based upon the trial results, Marcus explains that "adding rituximab to CVP chemotherapy in previously untreated patients with advanced follicular lymphoma results in a major improvement in all clinical endpoints," with minimal additional side effects. *Id*. at 7–8. According to Marcus, the combination therapy "significantly increased the duration of response, disease-free survival, and time to progression compared with that obtained in patients receiving CVP only." *Id*.

2. Analysis

Claims 1–3

As discussed above in Section II. C., we have determined, based on the record as a whole, that claims 1–3 are entitled to receive benefit of the '202 application filing date of August 11, 1999. As discussed *supra*, in

Section II. D., Marcus is a journal article that was not publicly accessible until 2005. Thus, Petitioner has not established that Marcus is prior art to claims 1–3. Consequently, Petitioner has not demonstrated, by a preponderance of the evidence that Marcus anticipates claims 1–3.

Claims 4–6

As discussed above in Section II. C., we have determined, based on the record as a whole, that claims 4–6 are not entitled to receive benefit of the '202 application filing date of August 11, 1999. Thus, for those claims, we recognize a priority date of June 15, 2012, the filing date of the '896 application. Accordingly, Marcus (2005) is prior art to claims 4–6.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987).

Petitioner asserts that Marcus discloses each element of claims 4–6. Pet. 38–44. Based on the record as a whole, we agree with Petitioner that Marcus teaches a method for treating follicular NHL comprising administering a therapeutically effective amount or rituximab during CVP therapy, wherein the method comprises administering 375 mg/m^2 of rituximab once every three weeks for eight doses. *Id*. at 38 (citing Ex. 1005, 3–4; Ex. 1002 ¶ 95). As Petitioner correctly asserts, those disclosures meet the limitations of independent claim 5, directed to administering "C2B8." Patent Owner recognizes that "C2B8" is a designation for rituximab and does not raise any substantive arguments regarding anticipation of claim 5 by Marcus. *See, e.g.*, PO Resp. 3 (addressing only claim 5 priority). Accordingly, based on the record as a whole, we determine that Petitioner

has shown by a preponderance of the evidence that Marcus anticipates independent claim 5.

Independent claim 4 recites an additional limitation, "wherein the method provides a beneficial synergistic effect in the patient." Petitioner asserts that Marcus discloses this element by reporting that patients receiving CVP in combination with rituximab demonstrated "major improvement in all clinical endpoints." Pet. 38 (citing Ex. 1005, 7). In particular, Petitioner relies on Marcus' statement that "[a]t a median follow-up of 30 months, the addition of rituximab to a standard CVP regimen significantly lengthened time to treatment failure and more than doubled time to progression, with significantly improved response rates, duration of response, disease-free survival, and time to next antilymphoma treatment." *Id*. (quoting Ex. 1005, 7).

In the Decision on Institution, we determined that Petitioner had not demonstrated a reasonable likelihood of prevailing in showing the unpatentability of claim 4 as anticipated by Marcus because Petitioner did not show that Marcus disclosed the combination of rituximab and CVP provides a greater beneficial effect than the additive effects of rituximab and CVP when administered alone. Dec. Inst. 15–16. Accordingly, we declined to institute an *inter partes* review of claim 4 as anticipated by Marcus. *Id*. at 16. Based, in part, on the same reason, we denied Petitioner's rehearing request regarding claim 4. Papers 14 and 25.

Subsequently, as discussed above in the Section I. (Introduction), we modified our Decision on Institution to include review of claim 4. Paper 39. Because that modification occurred after Patent Owner had filed its Patent Owner Response, we authorized Patent Owner to file a Supplemental Patent

Owner Response to address the newly instituted grounds, including anticipation of claim 4 by Marcus. Paper 40 (order), Paper 46 (Supplemental PO Response). Petitioner filed a Combined Reply to respond to Patent Owner's arguments in both the original and supplemental Patent Owner Responses. Paper 47. In this Final Written Decision, we consider whether, based upon the record as a whole, Petitioner has shown by a preponderance of the evidence that Marcus anticipates claim 4. *See Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1068 (Fed. Cir. 2016) ("[T]he Board is not bound by any findings made in its Institution Decision. At that point, the Board is considering the matter preliminarily without the benefit of a full record.").

Patent Owner asserts that because the Petition fails to show that Marcus disclosed a "beneficial synergistic effect," it has not and cannot establish that each and every limitation of claim 4 is met by Marcus. Supp. PO Resp. 19. In the Reply, Petitioner asserts that Patent Owner's argument elsewhere in the proceeding supports finding that Marcus meets that claim limitation. Reply 12. In particular, Petitioner asserts that Patent Owner "relies on a chart it used in prosecution to support its construction of 'beneficial synergistic effect.'" *Id*. (citing PO Resp. 16–17). Petitioner asserts that Patent Owner's chart "cites Marcus for its disclosure that R-CVP had a better than additive effect for the time to progression (TTP), as patients treated with R-CVP had a median TTP of 32 months, more than the sum of 15 months for CVP alone and 9 months for rituximab alone." *Id*. at 12–13 (citing Ex. 1005, 3–4; Pet. 41; Ex. 1002 ¶ 71). According to Petitioner, because the Petition and Petitioner's declarant, Dr. Lossos, rely upon the same data in Marcus for the disclosure of a "beneficial synergistic

effect," Petitioner has not waived the argument that Marcus discloses that limitation even under the Board's current construction. *Id*. at 13 (citing Pet. 38, 41; Ex. 1002 ¶ 71).

Based upon our review of the record as a whole, we agree with Petitioner that Marcus discloses each limitation of claim 4, and therefore anticipates the claim. To begin, we determine that Petitioner has shown that Marcus discloses a method for treating low grade or follicular NHL comprising administering a therapeutically effective amount of rituximab during a CVP therapy, wherein the method comprises administering 375 mg/m^2 of rituximab once every three weeks for eight doses for the same reasons discussed regarding claim 5.

Further, regarding the limitation requiring "the method provides a beneficial synergistic effect in the patient," we agree with Petitioner that Patent Owner's argument and evidence support Petitioner's contention that Marcus discloses that limitation too. In the Patent Owner Response, when discussing its proposed construction for the term "beneficial synergistic effect," Patent Owner refers to (and reproduces) a chart that Applicant relied upon during the prosecution of '896 Application. PO Resp. 16–17 (citing Ex. 1069, 121). Patent Owner introduces the chart by referring to Petitioner's argument that during prosecution Applicant argued that the 2006 Rituximab drug label and Marcus "showed that patients who received rituximab during CVP chemotherapy . . . 'demonstrat[ed] a beneficial synergistic effect in the patient[s].'" *Id*. at 16 (quoting Pet. 31). Patent Owner continues by stating "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

Ex. 1069, 121." PO Resp. 16–17. Patent Owner follows by asserting that "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." *Id.* at 17.

As discussed above, we agreed with Patent Owner's contention that the "beneficial synergistic effect" required "better than additive effects of rituximab and CVP administered alone." We also agreed with Patent Owner that Applicant's reference to the data reflected in the above chart supported that construction. We do not overlook the Marcus data identified and relied upon by Patent Owner in support of its proposed construction of a "beneficial synergistic effect" as we now consider whether Marcus discloses the very same limitation. As Patent Owner acknowledged, albeit in its claim construction discussion, Marcus discloses a median time to progression of 9 months for rituximab, 15 months for CVP, and 32 months for the rituximab-CVP combination therapy. Marcus 3–4; PO Resp. 17; Ex. 1069, 21. Referring to a chart containing that Marcus data representing "[a] comparison of certain therapeutic results achieved with rituximab alone, CVP alone, or the presently claimed combination," Ex. 1069, 9, Applicant explained, "[t]hese data point to the beneficial synergistic effect in the patient treated according to the presently claimed invention," *id.* at 10. We

agree and, thus, find that Marcus discloses "the method provides a beneficial synergistic effect in the patient," as required by claim 4. Accordingly, we conclude that Petitioner has shown by a preponderance of the evidence that Marcus anticipates claim 4.

Independent claim 6 recites a method for treating low grade or follicular NHL comprising administering "a chimeric anti-CD20 antibody," wherein such antibody "is produced from nucleic acid encoding a light chain variable region comprising the amino acid sequence in SEQ ID NO: 1 and a heavy chain variable region comprising the amino acid sequence in SEQ ID NO: 2, and comprises human gamma 1 heavy-chain and kappa light-chain constant region sequences." Petitioner asserts that limitation "is a description of the C2B8 chimeric antibody, which the '821 patent states is the preferred chimeric antibody," Pet. 42–43 (citing Ex. 1001, 3:3–5), and that the amino acid sequences disclosed in SEQ ID NO: 1 and SEQ ID NO: 2 "merely identify and characterize rituximab," also known as C2B8, *id*. at 39–40. As a result, Petitioner asserts that Marcus discloses the "chimeric anti-CD20 antibody" recited by claim 6 by disclosing rituximab. *Id*. at 39–40. Further, Petitioner asserts that Marcus discloses administering the antibody during CVP therapy in the manner required by claim 6 for the same reasons discussed regarding claim 5.

Patent Owner does not raise any substantive arguments regarding anticipation of claim 6 by Marcus. *See, e.g.*, PO Resp. 3 (addressing only claim 6 priority).

For the same reasons discussed regarding claim 5, we determine that Petitioner has shown that Marcus discloses a method for treating low grade or follicular NHL comprising administering a therapeutically effective

amount of rituximab during a CVP therapy, wherein the method comprises administering 375 mg/m^2 of rituximab once every three weeks for eight doses.

Further, we agree with Petitioner that Marcus discloses the "chimeric anti-CD20 antibody" recited by claim 6 by disclosing rituximab. It is undisputed that rituximab is also referred to as "C2B8" and that the '821 patent discloses C2B8 as a preferred chimeric anti-CD20 antibody. Ex. 1001, 3:3–5. As Petitioner explains, the description in claim 6 of the antibody "merely identif[ies] and characterize[s] rituximab." Pet. 40. Indeed, such characterizations include the amino acid sequences and the manner of production. Neither of those characterizations impart patentability to the claim. *See In re Crish*, 393 F.3d 1253, 1258–1259 (Fed. Cir. 2004) (identification and characterization of a prior art material in a claim do not render the claim directed to the known material patentable); *see also In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) (product in a claim is unpatentable if it is the same as the product of the prior art, even if the prior product was made by a different process). Ex. 1001, 3:3–5. Thus, we find that Marcus discloses each limitation of claim 6. Accordingly, we conclude that Petitioner has shown by a preponderance of the evidence that Marcus anticipates independent claim 6.

Based on the foregoing, we determine that Petitioner has shown by a preponderance of the evidence that claims 4–6 are unpatentable under 35 U.S.C. § 102(b) as anticipated by Marcus.

E. Obviousness over Marcus and the '137 Patent

Petitioner asserts that claims 3 and 6 would have been obvious over the combination of Marcus and the '137 Patent. Pet. 44–45.

1. The '137 Patent

The '137 patent issued on April 7, 1998, from an application that was filed on November 3, 1993. Ex. 1007. The '137 patent is directed to therapeutic treatment protocols for B cell lymphoma. Ex. 1007, Abstract. The patent characterizes rituximab and discloses the amino acid sequences of rituximab. *Id*. at Figs. 4 and 5 (SEQ ID NO: 6 and SEQ ID NO: 9).

2. Analysis

Claim 3

Petitioner relies on Marcus in the same manner discussed regarding the anticipation challenge of claim 3 and combines the '137 patent in the obviousness challenge for its disclosure of the amino acid sequence of rituximab. Pet. 44. As discussed above in Sections II. C. and E., Petitioner has not established that Marcus is prior art to claim 3. Consequently, Petitioner has not demonstrated, by a preponderance of the evidence that claim 3 is unpatentable over the combination of Marcus and the '137 patent.

Claim 6

As discussed above in Sections II. C. and E., Petitioner has demonstrated that Marcus is prior art to claim 6. Petitioner relies on Marcus in the same manner discussed regarding the anticipation challenge of claim 6 and combines the '137 patent in the obviousness challenge for its disclosure of the amino acid sequence of rituximab. Pet. 44. Patent Owner does not raise any substantive arguments regarding obviousness of claim 6 over Marcus and the '137 patent. *See, e.g.*, PO Resp. 3 (addressing only claim 6 priority).

Accordingly, for the same reasons discussed regarding the anticipation challenge of claim 6, we determine that Marcus taught each

limitation of claim 6. As this relates to an obviousness challenge, we next balance this determination with Patent Owner's asserted secondary considerations of nonobviousness.

Secondary Considerations

Patent Owner asserts that the claimed invention yields unexpected beneficial results with "long-term outcomes, including median Time To disease Progression ("TTP") and, relatedly, Progression-Free Survival ("PFS"), in LG/F-NHL patients using R-CVP." PO Resp. 67. Specifically, Patent Owner asserts that "the surprising benefits of this therapy include a vast improvement in median TTP [time to progression] reported, e.g., to increase from 15 months (with CVP alone) to at least 32 months when patients were treated with the claimed method of using 375 mg/m^2 of rituximab during CVP therapy." *Id*. at 68–69 (citing Ex. 1005, 4; Ex. 1069, 120–21). For the asserted unexpected PFS results, Patent Owner refers to rituximab's current prescribing information as reporting a PFS of 1.4 years with CVP alone and 2.4 years with R-CVP. *Id*. at 69 (citing Ex. 2015, 24, and Table 5).

As our reviewing court has instructed, to properly evaluate whether a superior property was unexpected, we must first consider what properties were expected. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). To do so, we consider the results of the closest prior art and compare them to those asserted for the claimed invention. *See In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.").

Regarding claim 6, Patent Owner does not clearly identify the closest prior art. We determine that the closest prior art regarding claim 6 is disclosed by Marcus, i.e., the combination of rituximab and CVP. Indeed, we have determined that Marcus anticipates claim 6. As we consider the obviousness challenge over Marcus, and Patent Owner's asserted surprising results, we do not find those results unexpected when compared to Marcus. Marcus reports the same beneficial synergistic effect that Patent Owner relies upon for its asserted unexpected results. In fact, Patent Owner cites Marcus as support for its assertion of unexpected TTP results. *See* PO Resp. 68–68 (citing Ex. 1005, 4).

Accordingly, we determine that Patent Owner has not demonstrated that the invention of claim 6 provides results that would have been unexpected when compared to the results of the same method disclosed by Marcus. As a result Patent Owner has not provided evidence of nonobviousness that outweighs our determination that the combination of Marcus and the '137 patent taught each limitation of the challenged claim.

Based on the foregoing, we determine that Petitioner has established by a preponderance of the evidence that claim 6 is unpatentable under 35 U.S.C. § 103(a) as obvious over Marcus and the '137 patent.

F. Obviousness over Czuczman, IDEC 10-K/A, Foon, and Dana

Petitioner asserts that claims 1–3 would have been obvious over the Czuczman, IDEC 10-K/A, Foon, and Dana. Pet. 45–54.

1. Czuczman

Czuczman is a journal abstract published in 1995 discussing the combination of the chimeric monoclonal anti-CD20 antibody IDEC-C2B8 (rituximab) and CHOP chemoimmunotherapy to treat low grade or follicular

lymphoma. Ex. 1011, 1, 3. Czuczman states that rituximab "has been shown to induce apotosis and to sensitize drug resistant human lymphoma cell lines to the cytotoxic effects of ricin and chemotherapeutic agents." *Id* at 3. Czuczman explains that the "rationale for combination of IDEC-C2B8 with CHOP includes: single agent efficacy, noncross-resistant mechanism of action, synergy with chemotherapeutic agents and non-overlapping toxicities." *Id*.

In Czuczman's study, patients were given a dose of 375 mg/m^2 on weeks 1, 7, 13, 20, and 21 (6 doses). *Id*. Czuczman reports that the "[o]verall response rate for the 14 pts completing all scheduled therapy to date is 100%." *Id*. Additionally, Czuczman reports that four of the seven patients "known to be positive for bcl-2" have completed treatment and all four "have converted to bcl-2 negativity." *Id*. Standard chemotherapy regimens alone, including CHOP, have previously been unable to clear bcl-2 positivity from marrow. *Id*. According to Czuczman, its study finding of molecular remissions "suggests that the anti-tumor activity of CHOP and IDEC-C2B8 is superior to CHOP therapy alone." *Id*.

2. IDEC 10-K/A

IDEC 10-K/A is an annual report filed with the U.S. Securities and Exchange Commission ("SEC") by IDEC Pharmaceuticals Corporation. Ex. 1006, 1. The report states that "Phase II studies suggest that Rituxan may also be useful in combination with chemotherapy in low grade or follicular lymphomas . . . ." *Id*. at 12. Additionally, the report explains that several rituximab post-marketing trials "will explore the use of Rituxan in a variety of investigational B-cell non-Hodgkin's lymphoma clinical settings including: (i) combination therapy with widely used chemotherapy regimens

for both low grade and intermediate/high grade disease." *Id*. at 13.

3. Foon

Foon is a chapter on lymphomas published in Williams Hematology in 1995. Ex. 1008, 3, 23. Foon provides a table listing three combination agents used to treat low grade lymphoma: CVP, CHOP, and COPP (cyclophosphamide, vincristine, procarbazine, and prednisone). *Id*. at 29. Foon explains that similar to CVP,

"regimens including doxorubicin have demonstrated excellent responses for patients with follicular small cleaved cell lymphoma," as compared to single-agent alkylating therapy, "but there is no evidence that such treatment prolongs survival." *Id*. at 30.

4. Dana

Dana is a journal article published in 1993 discussing a comparison of the effectiveness of CHOP on overall survival in patients with low grade NHL compared with the effectiveness of less-aggressive CVP programs. Ex. 1009, Abstract, 6. Dana explains that for patients with small lymphocytic lymphoma and follicular small cleaved-cell lymphoma, results of administering CHOP are "comparable" to those achieved with CVP. *Id*. at 6. According to Dana, those results indicate that "the addition of doxorubicin to CVP [i.e., CHOP] results in no improvement in survival." *Id*.

5. Analysis

As previously discussed above in Section II. D., we have determined that Petitioner has shown by a preponderance of the evidence that Czuczman, Foon, and Dana are printed publications accessible prior to the priority date recognized for claims 1–3. Here, Patent Owner challenges the

sufficiency of Petitioner's showing regarding the printed publication status of IDEC 10-K/A with respect to Petitioner's claim challenge based upon that reference in combination with Czuczman, Foon, and Dana. Thus, we begin our analysis by considering whether Petitioner has met that burden. *See Medtronic, Inc. v. Barry*, 891 F.3d 1368, 1380 (Fed. Cir. 2018) (petitioner bears burden of establishing by a preponderance of the evidence that an asserted reference is a printed publication).

Printed Publication Status of IDEC 10-K/A

In the Decision on Institution, we determined that Petitioner had not shown that IDEC 10-K/A is a prior art printed publication and, thus, we did not consider that reference in Petitioner's Czuczman obviousness challenges. Dec. Inst. 21. Subsequently, as discussed in Section I. (Introduction), we modified our Decision on Institution to include review of the Czuczman grounds, including IDEC 10-K/A. Paper 39. Because that modification occurred after Patent Owner had filed its Patent Owner Response, we authorized Patent Owner to file a Supplemental Patent Owner Response to address the newly instituted grounds, including IDEC 10-K/A. Paper 40 (order), Paper 46 (Supplemental PO Response). Petitioner filed a Combined Reply to respond to Patent Owner's arguments in both the original and supplemental Patent Owner Responses. Paper 47. In this Final Written Decision, we consider whether Petitioner has shown by a preponderance of the evidence that IDEC 10-K/A is a prior art printed publication.

According to Petitioner, IDEC 10-K/A was publicly available in the SEC's Electronic Data Gathering, Analysis, and Retrieval system ("EDGAR") by at least March 3, 1998. Pet. 33. Petitioner asserts that federal securities law requires that "the information contained in any

registration statement, application, report, or other document filed with the Commission . . . shall be made available to the public." *Id*. at 15 n.6 (quoting 15 U.S.C. § 80a-44). Petitioner asserts further that "[t]he EDGAR Filing Details indicate that the IDEC 10-K/A was accepted and filed on March 3, 1998." *Id*. at 33 n.11 (citing Ex. 1056). As additional support, Petitioner states that "[t]he EDGAR Filer Manual from September 1996 explains that the public portions of live filings, such as the IDEC 10-K/A, are 'immediately disseminated to the public.'" *Id*. (citing Ex. 1055, 20).

Patent Owner contends that Petitioner has not established that IDEC 10-K/A is a prior art printed publication. Supp. PO Resp. 4. According to Patent Owner, the evidence Petitioner relies upon to show public accessibility of IDEC 10-K/A, i.e., the EDGAR Filer Manual (Ex. 1055) and the EDGAR Filing Details (Ex. 1056), does not establish that IDEC 10-K/A was catalogued or indexed in a way that might establish public accessibility on the date Petitioner claims. *Id*. Additionally, Patent Owner asserts that, even if the reference was catalogued or indexed, Petitioner has not presented any evidence that a person of ordinary skill in the art would expect to look for, or find, IDEC 10-K/A when seeking guidance on how to treat NHL patients. *Id*.

In the Reply, Petitioner asserts that SEC filings have been recognized as prior art disclosures in other *inter partes* reviews. *Id*. at 11 (citing *Apotex Inc. v. OSI Pharm., LLC*, IPR2016-01284, Paper 49 at 21 (P.T.A.B. Jan. 8, 2018) (finding an ordinary artisan would have looked to 10-K to learn drugs and treatments pharmaceutical companies were working on at the time of invention); *CFAD (Adroca) LLC v. Acorda Therapeutics, Inc.*, IPR2015-01853, Paper 13 at 7–8 (P.T.A.B. Mar. 11, 2016) (finding company's S-1

registration statement was a printed publication based on news publications that indicated the company had performed clinical trials with the claimed agent). Those cases cited by Petitioner have not been designated as precedential and are not controlling. Indeed, as Patent Owner notes, the Board has determined in other instances that Petitioner has not established adequately that an SEC 10-K/A filing was prior art. *See, e.g.*, Supp. PO Resp. 4 (citing *Liberty Mut. Ins. Co. v. Progressive Cas. Ins. Co.*, CBM2013-00009, Paper 68, 18–20 (Feb. 11, 2014) (finding the "Geostar 10-K" form was not a printed publication because Petitioner did not explain how such forms are indexed or catalogued or how else the public may search the technical content contained in such forms)). As we discussed above in Section II. C., a reference is deemed "'publicly accessible' upon a satisfactory showing that such document 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," *SRI Int'l, Inc.*, 511 F.3d at 1194. This determination is made on a case-by-case basis, in view of the record evidence.

In the Reply, Petitioner further responds to Patent Owner's arguments by asserting that, "by mandatory operation of the SEC's EDGAR system, the 10-K/A was published and searchable – as further supported by the Hall-Ellis declaration." Reply 11 (citing Ex. 1303 ¶¶ 62–69). According to Petitioner, "IDEC was required to publish the 10-K/A to the EDGAR system, this system was routinely searchable, and a POSA would have had no difficulty in accessing this information." *Id*. (citing Ex. 1303 ¶¶ 64–65). Petitioner asserts also that Dr. Lossos explained that "IDEC issued press releases in December 1996 announcing its intention to combine rituximab

with other anti-cancer treatments." *Id*. at 11–12 (citing Ex. 1002 ¶ 61). According to Petitioner, "IDEC's press releases and other scientific publications about the promise of rituximab were sufficient to motivate a POSA to seek IDEC company filings like Ex. 1006 that reported planned uses of rituximab." *Id*. at 12.

Having considered the evidence and arguments, we conclude that Petitioner has not established adequately that IDEC10-K/A is a prior art printed publication. Petitioner's evidence that IDEC 10-K/A was filed on EDGAR, i.e., the EDGAR Filer Manual (Ex. 1055), the EDGAR Filing Details (Ex. 1056), and the cited testimony of Dr. Hall-Ellis (Ex. 1303 ¶¶ 64–65), demonstrates, at most, that IDEC 10-K/A was published and available to the public in a searchable database. However, Petitioner has not explained or demonstrated that a person interested in treating NHL and ordinarily skilled in the subject matter of doing so, exercising reasonable diligence, would have known to locate such information in an SEC filing, or specifically in IDEC 10-K/A. *See SRI Int'l, Inc.*, 511 F.3d at 1194. Indeed, Petitioner does not assert that any of Exhibits 1002, 1006, 1055, 1056, or 1303 provide such information. Exhibit 1006 is IDEC 10-K/A. Exhibits 1055, 1056, and 1303 are directed to the availability of that reference in EDGAR. Petitioner relies upon the testimony of Dr. Hall-Ellis when asserting that "a POSA would have had no difficulty in accessing this information." Reply 11 (citing Ex. 1303 ¶¶ 64–65). However, we note that the cited testimony of Dr. Hall-Ellis does not include any discussion regarding what information or databases the person of ordinary skill in the art of treating NHL would have searched.

Similarly, the testimony of Dr. Lossos in Exhibit 1002, cited by Petitioner, does not address that point. Rather, Dr. Lossos discusses a December 1996 press release by IDEC describing an ongoing Phase II trial combining rituximab with CHOP and its plan to study rituximab in combination with other anti-cancer treatments. Ex. 1002 ¶ 61. According to Petitioner, "IDEC's press releases and other scientific publications about the promise of rituximab were sufficient to motivate a POSA to seek IDEC company filings like Ex. 1006 that reported planned uses of rituximab." Reply 12. However, Petitioner's evidence does not establish that fact. Indeed, Dr. Lossos does not address or draw that conclusion. *See* Ex. 1002 ¶ 61. Further, as Patent Owner asserts, *see* Paper 52, 2, Petitioner has not identified what "other scientific publications" it refers to in that argument. Nor does Petitioner identify more than one press release. *See* Reply 12 (referring to multiple "IDEC's press releases"). Moreover, for the identified December 1996 press release, Petitioner has not asserted or explained any details regarding such release, or identified in the release any information that would have led a person of skill in the art, exercising reasonable diligence, to pursue an SEC filing for further information. *See, e.g.*, Pet. 15, Reply 12.

Thus, based upon our consideration of the record as a whole, and for the foregoing reasons, we find that Petitioner has not shown that IDEC 10-K/A was publicly accessible as required to be considered a prior art printed publication. Accordingly, we conclude that Petitioner has not shown by a preponderance of the evidence that IDEC 10-K/A is a printed publication. Therefore, we analyze Petitioner's remaining grounds without considering the teachings of IDEC 10-K/A, as Petitioner has not established that

reference as prior art to the challenged claims.[19]

Obviousness over Czuczman, Foon, and Dana

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id*. at 417.

Claims 1–3 are directed to treating low grade or follicular NHL comprising administering to a patient 375 mg/m^2 of a chimeric anti-CD20 antibody (claim 3), namely, rituximab (claim 1), i.e., C2B8 (claim 2), in combination with CVP therapy. Claim 1 additionally requires that such method "provides a beneficial synergistic effect in the patient," and claim 3 recites that the antibody is "produced from nucleic acid" encoding amino acid sequences in SEQ ID NO: 1 and SEQ ID NO: 2.

There is no dispute that Czuczman alone teaches a method for treating low grade or follicular NHL comprising administering to a patient a therapeutically effective amount of IDEC-C2B8, i.e., 375 mg/m^2, during a chemotherapeutic regimen, as required, in part, by claims 1–3. Nor is it

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[19] Patent Owner asserts that *SAS* and Office policy prevent us from considering the combined teachings of Czuczman, Foon, and Dana. *See* Supp. PO Resp. 6. We disagree. The Federal Circuit has explained the impact of *SAS*, and observed that such impact relates to our consideration of Decisions on Institution. *See, e.g.*, *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (explaining that *SAS* "require[s] a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition."). Neither *SAS* nor our Office Guidelines limit *how* we consider all patent claims and grounds in a Final Written Decision.

disputed that a person of skill in the art would have understood Czuczman's reference to IDEC-C2B8 meets the claim recitations of "rituximab" (claim 1), "C2B8" (claim 2) and "chimeric anti-CD20 antibody produced from nucleic acid encoding a light chain variable region comprising the amino acid sequence in SEQ ID NO: 1 and a heavy chain variable region comprising the amino acid sequence in SEQ ID NO: 2, and comprises human gamma 1 heavy-chain and kappa light-chain constant region sequences" (claim 3). The chemotherapeutic regimen disclosed in Czuczman is CHOP.

The points of contention between the parties center upon whether Petitioner has established by a preponderance of the evidence that (a) a person of skill in the art would have been motivated to modify Czuczman's method by substituting CVP (cyclophosphamide, vincristine, and prednisone) for CHOP based upon the teachings and suggestions of combined prior art, and (b) such modification would have been reasonably expected to successfully treat low grade or follicular NHL. Further, regarding claim 1, the disputes extend to whether, in view of Czuczman, Foon, and Dana, Petitioner has shown by a preponderance of the evidence that a person of skill in the art at the time of the invention would have reasonably expected that substituting CVP for CHOP would successfully provide a "beneficial synergistic effect" in the patient. Accordingly, we consider those contentions, along with Patent Owner's asserted secondary considerations, in our following discussion.

Motivation to Substitute CVP for CHOP

Apart from relying upon any suggestion in IDEC 10-K/A for combining rituximab with chemotherapy regimens to treat low grade NHL,

see Pet. 46–47, 51, which we do not consider here, Petitioner asserts that a person of skill in the art would have been motivated to modify Czuczman's method of treating low grade NHL by combining rituximab with CVP in place of CHOP because Foon and Dana explain that, similar to CHOP, CVP was also considered a standard chemotherapy regimen for treating low grade NHL. Pet. 51. Petitioner asserts further that a person of ordinary skill in the art would have understood from Foon and Dana that, while "equally effective" in treating low grade NHL, CVP is less toxic than CHOP because, unlike CHOP, CVP does not include doxorubicin and therefore lacks the toxicity associated with doxorubicin. *Id*. (citing Ex. 1002 ¶¶ 108–109). According to Petitioner, in light of that knowledge, along with Dana's teaching that "doxorubicin provides no added benefit to low-grade NHL patients, a POSA would have been encouraged by Dana to use CVP instead of Czuczman's CHOP in combination with rituximab." *Id*.

Additionally, Petitioner asserts that "Applicant's argument during examination of the '896 application that matured into the '821 patent supports the conclusion that it would have been obvious to a POSA to combine CVP—a standard chemotherapy regimen—with rituximab in light of the prior art." Pet. 52. In particular, Petitioner asserts that in response to the examiner's argument that the '202 priority application did not disclose combining rituximab with CVP, Applicant explained that its "'combination therapy' disclosure was not confined to particular chemotherapy regimens, but was a general teaching that the skilled person would have known to apply the CVP chemotherapy," and that CVP was one of three exemplified regimens (CVP, CHOP, cyclophosphamide) for treating low grade NHL. *Id*. (quoting Ex. 1069, 162).

Further, Petitioner asserts that "Czuczman also provides a rationale for combining rituximab with CHOP that a POSA would have understood to apply equally to CVP: 'single agent efficacy, non cross-resistant mechanisms of action, synergy with chemotherapeutic agents and non-overlapping toxicities.'" *Id*. at 53–54 (quoting Ex. 1011, 3; citing Ex. 1002 ¶ 112).

Patent Owner asserts that, without IDEC 10-K/A, Petitioner has not shown that a person of ordinary skill in the art would have been motivated to modify Czuczman by substituting CVP for CHOP. PO Resp. 22. According to Patent Owner, Petitioner "asserted EX1006 [IDEC 10-K/A] 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." *Id*. (citing Pet. 45, 48; Ex. 1002 64–65, 102–112). Patent Owner asserts that "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." *Id*. at 23.

We disagree with Patent Owner. Petitioner provided a number of motivations for combining rituximab with CVP that did not involve or require consideration of IDEC 10-K/A. Regarding Foon and Dana, Petitioner explained that a person of skill in the art would have understood from those references that CVP was a well-known alternative for treating low grade NHL at the time of the invention was CVP. Pet. 47, 51. We agree with that characterization of Foon and Dana by Petitioner. Foon provided a table listing agents used to treat low grade lymphoma. The table includes two lists: "Single Agents," such as chloramubucil and

cyclophosphamide, and "Combination Therapies," including only three therapies, i.e., CHOP, CVP, and COPP. Ex. 1008, 29 (Table 111-7)). Thus, we find that Foon would have suggested to a person of skill in the art that treatment of low grade NHL with a "combination therapy" involved three alternatives, CHOP, CVP, or COPP. Dana focused on CHOP, the doxorubicin-containing therapy, and compared that combined therapy with "less-aggressive programs," such as CVP. Ex. 1009, 2 and 6. Dana concluded that in small-cell and follicular NHL, "the addition of doxorubicin to CVP results in no improvement in survival." *Id*. at 6.

Petitioner relied also upon Czuczman as providing motivation for its proposed substitution. Specifically, Petitioner asserts that a person of skill in the art would have understood that Czuczman's rationale for combining rituximab with CHOP would have applied equally to CVP, i.e., "single agent efficacy, non cross-resistant mechanisms of action, synergy with chemotherapeutic agents and non-overlapping toxicities." Pet. 53–54 (quoting Ex. 1011, 3; citing Ex. 1002 ¶ 112).

Patent Owner asserts that a person of skill in the art would not have found motivation in Czuczman to substitute CVP for CHOP because "Czuczman focuses exclusively on combining rituximab with CHOP" and "suggested nothing concerning other chemotherapies (much less CVP)." PO Resp. 24 (citing Ex. 2029 ¶¶ 54–55). Patent Owner, however, reads Czuczman and Petitioner's arguments too narrowly. That Czuczman does not mention CVP misses the point. Petitioner does not allege that Czuczman discloses the combination of rituximab and CVP. Rather, Petitioner asserts that Czuczman provides a rationale for combining rituximab and CHOP that has a broader applicability to other known chemotherapeutic agents,

including CVP.

Patent Owner has not asserted any arguments or evidence that a person of skill in the art would not have considered Czuczman's motivating factors involving "single agent efficacy," "non cross-resistant mechanisms of action," and "non-overlapping toxicities" to apply similarly to CVP. Patent Owner's arguments instead are directed toward Czuczman's disclosed motivation based upon "synergy with chemotherapeutic agents." In any event, we find that the three additional reasons discussed by Czuczman would have been sufficient to motivate a person of skill in the art to consider other low grade NHL therapies with similar attributes to combine with rituximab, including CVP.

Patent Owner asserts that a person of skill in the art would have been discouraged from Petitioner's proposed substitution based on Czuczman's teaching that its rituximab-CHOP regimen yielded a 100% response rate and conversion to bcl-2 negativity. PO Resp. 25 (citing Ex. 1011, 3: Ex. 2029 ¶ 56). According to Patent Owner, those endpoints "were understood to be worse for CVP as compared to CHOP," *id*. at 25–26 (citing Ex. 2029 ¶ 57) and that a "POSITA would not have anticipated that R-CVP would result in bcl-2 conversion," *id*. at 26–27. Patent Owner asserts also that the doxorubicin component of CHOP "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." *Id*. at 26 (citing Ex. 1041, 3; Ex. 1079, 8; Ex. 2029 ¶¶ 58, 44–45).

We disagree with Patent Owner that Czuczman discourages or teaches away from Petitioner's proposed modification by describing the response

rate and bcl-2 conversion of the rituximab-CHOP therapy. Rather, we find that those teachings would likely encourage a person of skill in the art to pursue additional rituximab-chemotherapy combinations. Czuczman explained that standard induction or salvage chemotherapy regimens alone, e.g., CHOP, were unable to clear bcl-2 positivity from marrow. Ex. 1011, 3. It was the combination of rituximab with the CHOP regimen that resulted in the bcl-2 conversion. *Id*. Similarly, the response rates reported by Czuczman were attributable to the rituximab-CHOP therapy and not CHOP alone. Thus, we find that those results would have suggested, and not discouraged, a person of skill in the art to combine rituximab with other chemotherapy regimens to achieve bcl-2 conversion and to improve response rates. Patent Owner does not identify, nor do we see, any disclosure in Czuczman teaching or suggesting that those endpoints are attributable to the presence of doxorubicin in CHOP. Insofar as Patent Owner relies upon a later Czuczman publication describing the rationale for combining rituximab with CHOP as including "known synergy with doxorubicin," Ex. 2029 ¶ 45 (quoting Ex. 1041, 3), Patent Owner and Dr. McLaughlin have not identified any disclosure in that reference attributing the bcl-2 conversion and/or response rate specifically to that (or any) rationale for the combination of rituximab and CHOP.

Moreover, we note that the later Czuczman publication also discloses rituximab's "synergistic antitumor activity with certain chemotherapeutic agents (including doxorubicin)." Ex. 1041, 3. Thus that publication did not limit rituximab to synergy with doxorubicin as Patent Owner suggests. Rather, when adapting the synergy discussion to a rituximab combination with CHOP, the reference highlights the synergy with doxorubicin as part of

its rationale for the combination. *Id*.

Additionally, Patent Owner asserts that "while no cure for LG/F-NHL existed, CHOP was known to be curative in certain NHLs and was thus favored for combining with rituximab to achieve durable responses." PO Resp. 26 (citations omitted) (citing Ex. 2029 ¶ 59). However, neither Patent Owner nor its declarant, Dr. McLaughlin, supports that assertion with evidence. Even if CHOP was known to be "curative in certain NHLs," neither Patent Owner nor Dr. McLaughlin explains why such effectiveness in another (unidentified) type of NHL would be considered favorable alone or in combination with rituximab to treat low grade or follicular NHL.

Regarding Foon and Dana, Patent Owner asserts that those references did not disclose chemoimmunotherapy combinations including CVP. PO Resp. 28–29. In support, Patent Owner asserts that Foon combined interferon-α with CHOP-bleomycin or COPA, and Dana disclosed CHOP-BCG. *Id*. Further, Patent Owner asserts that at the time of invention "it was unpredictable whether particular combinations with immunotherapies would even be additive, let alone synergistic as Claim 1 requires." *Id*. at 29 (citing Ex. 2029 ¶ 70). In support, Patent Owner refers to Foon's reports that certain of its interferon-α and interleukin-2 immunotherapy combinations "did not necessarily lead to additive or even neutral results." *Id*. Additionally, Patent Owner asserts that "neither Foon nor Dana ever suggests combining rituximab with CVP," and that Petitioner's selection of CVP from the other chemotherapy options disclosed by Foon and Dana as an alternative to CHOP is based on nothing but hindsight. *Id*. at 30–32.

Patent Owner's arguments again miss the point. Petitioner does not rely upon Foon or Dana as suggesting a particular chemoimmunotherapy

combination. Rather, Petitioner relies on those references for their teachings relating to CVP as a known alternative to CHOP for treating low grade NHL. Patent Owner and Dr. McLaughlin have not explained persuasively how Foon's reports relating to interferon-α and interleukin-2 immunotherapy combinations serve to inform a person of skill in the art about the predictability of a rituximab therapy combination. Nor do we see that an object of Foon is to do so. Further, we disagree with Patent Owner's assertion that Petitioner's selection of CVP as an alternative to CHOP is based only on hindsight. As discussed, *supra*, Foon and Dana relate those two regimens as alternative therapies for low grade NHL, with Foon identifying those regimens as two of three such combination therapies at the time of the invention.

Patent Owner asserts also that to modify Czuczman's regimen, a "POSITA would have needed, *inter alia*, an expectation that an alternative agent would yield more favorable results" than the molecular complete remission, 100% response rates, and encouraging toxicity data Patent Owner asserts that Czuczman reported. PO Resp. 35 (citing Ex. 2029 ¶¶ 86–87). According to Patent Owner, Petitioner failed to show that a person of skill in the art would have expected R-CVP and R-CHOP to be "less toxic and equally effective." *Id*. at 35–40. Patent Owner asserts that Czuczman, Foon, and Dana do not address the relative toxicities of CVP and CHOP. *Id.* at 38–39. Additionally, Patent Owner asserts that Petitioner has not addressed the comparative toxicity of CVP and CHOP based upon the relative amounts of cyclophosphamide required in each of those regimens to treat low grade NHL. *Id*. at 39–40. Patent Owner asserts that even if CVP was considered less toxic than CHOP, "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 chlorambucil identified in Foon and Dana. *Id*. at 40. According to Patent Owner, a person motivated by lower toxicity would have considered replacing CHOP with chlorambucil or mini-CHOP. *Id*. at 41–42.

Patent Owner is mistaken in asserting that modifying Czuczman's combination therapy would have required a person of skill in the art to have "an expectation that an alternative agent would yield more favorable results." PO Resp. 35. *See In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) ("[J]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes."). We have determined that Petitioner has demonstrated by a preponderance of the evidence that a person of skill in the art would have understood from Foon and Dana that CHOP and CVP were two of three combination therapies that were known at the time of the invention to be useful for treating low grade NHL. Thus, even if CVP does not offer a better toxicity profile or greater efficacy with respect to certain endpoints, e.g., response rate and bcl-2 conversion, than CHOP, Petitioner's proposed modification of Czuczman amounts to no more than a simple substitution of one known and useful chemotherapy for treating low grade NHL for another. *See KSR*, 550 US at 416–17 (addressing claimed subject matter involving no more than the simple substitution of one known element for another). Moreover, we find that Petitioner has further demonstrated by a preponderance of the evidence that a person of skill in the art would have had a reason to combine rituximab with CVP based upon *at least* three of the four elements described by Czuczman as its rationale for combining rituximab with CHOP, i.e.,

"single agent efficacy," "non cross-resistant mechanisms of action," and "non-overlapping toxicities." Further, as discussed below, we determine a person of skill in the art would have considered Czuczman's disclosure of "synergy with chemotherapeutic agents" to similarly serve as a rationale for combining rituximab with CVP.

Reasonable Expectation of Success

Petitioner asserts that Czuczman's disclosed rationale for combining rituximab with CHOP would have supplied a person of skill in the art with a reasonable expectation that rituximab administered during a CVP regimen would also be efficacious. Pet. 54 (citing Ex. 1002 ¶ 112); Ex. 1011, 3.

Patent Owner asserts that Petitioner fails to establish a reasonable expectation of success in substituting CVP for CHOP in Czuczman for some of the same reasons Patent Owner asserted that a person of skill in the art would not have been motivated to make the substitution. PO Resp. 44–45. In particular, Patent Owner asserts that "the Petition failed to establish [that a] POSITA starting with Czuczman would have had any reasonable expectation of success in achieving 'equal efficacy' by substituting CVP for CHOP" because Petitioner relied only upon overall survival of CVP alone without considering the overall response rate and bcl-2 conversion reported by Czuczman for the combination of rituximab with CHOP. *Id*. at 45–50. According to Patent Owner, "at best, Petitioner's evidence suggests 'no difference' between CVP and CHOP." *Id*. at 45 (citing Pet. 9–10; Ex. 2027, 38:20–24; Ex. 2029 ¶ 107).

Patent Owner's arguments that Petitioner has not shown that the combination of rituximab and CVP would be better or the same as Czuczman's combination of rituximab and CHOP are misdirected. To

begin, based upon our reading of Czuczman, the object of the study was to determine whether the combination of rituximab and CHOP provided a tolerable and effective chemoimmunotherapy for low grade lymphoma. Ex. 1011. The authors describe their rationale for combining those agents, wherein each aspect of the rationale provides a basis for expecting that the combination will be successful. For example, "single agent efficacy" suggests that both rituximab and CHOP were known to be effective in treating low grade lymphoma; "non-cross resistant mechanism of action" suggests that when administered as part of the same regimen, the two agents would not be expected to interfere with the action of the other; "non-overlapping toxicities" suggests that the agents together will not result in increased, overlapping toxicities; and "synergy with chemotherapeutic agents" suggests that rituximab has been shown to demonstrate synergy with other chemotherapy and may be expected to do so with CHOP also. *See* Ex. 1011. Thus, we do not read Czuczman as a study with an objective to achieve a specific response rate or bcl-2 conversion. Rather, those results were reported to demonstrate how the chemoimmunotherapy was effective in treating low grade or follicular NHL.

More to the point, the proper inquiry regarding a reasonable expectation of success involves considering whether a person of skill in the art would have had a reasonable expectation of successfully making the *claimed invention* in light of the prior art. *See Amgen, Inc. v. F. Hoffman–La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art.") (citing *In re Kubin*, 561 F.3d 1351, 1360 (Fed.Cir.2009)

("[S]tated in the familiar terms of this court's longstanding case law, the record shows that a skilled artisan would have had a resoundingly 'reasonable expectation of success' in deriving the claimed invention in light of the teachings of the prior art.")). Thus, the issue here is not whether the proposed modification of Czuczman would be expected to provide the same specific response rate or bcl-2 conversion as Czuczman reported for its rituximab-CHOP therapy. Rather, the appropriate inquiry, regarding our analysis of claims 2 and 3 (which do not require a "beneficial synergistic effect"), is whether a person of skill in the art would have reasonably expected the modified rituximab-CVP therapy to successfully treat low grade lymphoma, by any measure, as claimed.

Based on our consideration of the record as a whole, we find that Petitioner has demonstrated by a preponderance of the evidence that a person of skill in the art would have had a reasonable expectation of success in treating low grade NHL when modifying Czuczman's method by combining rituximab with CVP in place of CHOP. Patent Owner challenges whether a person of skill in the art would have considered Czuczman's synergy disclosure as applicable to CVP, and we address that argument below. Patent Owner, however, does not challenge the applicability of the remaining three factors involved in Czuczman's rationale to CVP. We find that those unchallenged factors alone demonstrate persuasively that a person of skill in the art would have had a reasonable expectation of successfully treating low grade NHL with a chemoimmunotherapy comprising administering rituximab and CVP, as required by claims 2 and 3. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[C]ase law is clear that obviousness cannot be avoided simply by a showing of some

degree of unpredictability in the art so long as there was a reasonable probability of success. . . . [T]he expectation of success need only be reasonable, not absolute." (citations omitted)).

Regarding the additional requirement in claim 1 that the method of administering rituximab and CHOP provides a "beneficial synergistic effect," Petitioner relies upon Czuczman's teaching that rituximab was known to have "synergy with chemotherapeutic agents" to support its contention that an ordinarily skilled artisan would have had a reasonable expectation of success in making the invention in light of the prior art. Pet. 53–54 (citing Ex. 1011, 3; Ex. 1002 ¶ 112).

Patent Owner asserts that a person of skill in the art would not have reasonably expected that replacing CHOP with CVP in Czuczman's method would yield a "beneficial synergistic effect." PO Resp. 50. In particular, Patent Owner asserts that although Czuczman uses the word "synergy," the reference fails to disclose a "beneficial synergistic effect," under the proper construction, because Czuczman's study did not compare the effects of the rituximab-CHOP regimen with the effects of CHOP alone and rituximab alone. *Id*. at 51–52. According to Patent Owner, a "POSITA could not determine from Czuczman whether the combination's response rate [or bcl-2 conversion rate] is better than the additive effects of CHOP and rituximab alone." *Id*. at 52.

Additionally, Patent Owner asserts that Czuczman's reference to "synergy with chemotherapeutic agents" did not concern the findings of Czuczman's study, but instead referred to *in vitro* experiments by Demidem 1995 "evaluating the ability of rituximab to 'sensitize' cell lines to certain chemotherapeutic agents, including by 'pre-treatment.'" Pet. 53 (citing to

Ex. 1041, 3; Ex. 1078; Ex. 1079, 8 (Table 2); Ex. 2029 ¶ 122). Specifically, Patent Owner asserts that Demidem 1995 and Demidem 1997 describe studies relating to "sensitization" and do not refer to the type of synergy required by claim 1. *Id*. at 53. In particular, Patent Owner notes that "Demidem [1995] does not use the word 'synergy' even once, and even Petitioner's expert now concedes Demidem [1995] does not teach synergy under the proper construction." *Id*. at 53–54 (citing Ex. 2027, 89:4–13).

Further, Patent Owner asserts that "Demidem [1995] does not disclose or discuss sensitization to *all* chemotherapeutic agents, and never mentions sensitization to *any* component of CVP." *Id*. at 54 (citing Ex. 1078). Additionally, Petitioner asserts that the "additional Demidem paper proffered by Petitioner further confirmed rituximab did not sensitize lymphoma cells *in vitro* for all chemotherapeutic agents" by disclosing that rituximab sensitized the cancer cells to cisplatin and doxorubicin, but not etoposide. *Id*. (citing Ex. 1079, 8; Ex. 2029 ¶ 123). According to Patent Owner "[a]s any POSITA would have recognized from these documents, the Demidem authors did not test C, V, or P in their sensitization assay," or determine whether the sensitization observed was better than additive effects of each agent alone. *Id*. at 54–55 (citing Ex. 2020 ¶ 124).

Additionally, Patent Owner asserts that because "the Demidem references do not discuss any *in vivo* clinical outcomes," they could not disclose a "beneficial synergistic effect." *Id*. at 55 (citing Ex. 2029 122–125; Ex. 2027, 89:4–13).

Based on our consideration of the record as a whole, we find that Petitioner has demonstrated by a preponderance of the evidence that a person of skill in the art would have had a reasonable expectation of success in providing a beneficial synergistic effect when modifying Czuczman's method by combining rituximab with CVP in place of CHOP, as required by claim 1. As Petitioner asserts, Czuczman describes rituximab as having "synergy with chemotherapeutic agents." Pet. 54; Ex. 1011, 3. We find that Czuczman does so without qualifying or limiting that disclosure to CHOP or other doxorubicin-containing chemotherapy. Insofar as Patent Owner asserts otherwise, PO Resp. 53 n.21, that argument is inadequately supported as Patent Owner has not identified any portion of Czuczman or Demidem 1995, cited therein, limiting Czuczman's synergy statement to CHOP or doxorubicin-containing chemotherapy.

Patent Owner contends also that Czuczman's use of the word "synergy" does not disclose a "beneficial synergistic effect" because Czuczman's study did not compare the effects of the rituximab-CHOP regimen with the effects of CHOP alone and rituximab alone. PO Resp. 51–52. However, as Patent Owner correctly asserts elsewhere, Czuczman's reference to "synergy with chemotherapeutic agents" was included as background information that provided a rationale for initiating Czuczman's study, and was not a characterization of Czuczman's results. *See id.* at 53.

Patent Owner additionally asserts that Czuczman's reference to "synergy with chemotherapeutic agents" does not refer to the type of synergy required by claim 1 because it relates to experiments by Demidem 1995. PO Resp. 53. According to Patent Owner, both Demidem 1995 and Demidem 1997 are directed to studies demonstrating drug "sensitization."

Further, Patent Owner asserts that those studies were *in vitro* and do not discuss any *in vivo* clinical outcomes, so they could not disclose a "beneficial synergistic effect." *Id*. at 55.

We disagree with Patent Owner as to both points, based upon our construction of the term "beneficial synergistic effect." In construing that term, we relied on the Specification disclosure that a synergistic therapeutic composition is one "wherein the therapeutic effect is better than the additive effects of either therapy administered alone." Ex. 1001, 3:44–47. Further, we found that the Specification recognized the study disclosed in Demidem 1997 as a specific example of achieving a "beneficial synergistic effect" via sensitization and potentiation of the studied cell line. As Patent Owner recognized Demidem 1995 as reporting the same sensitization, we find that reference exemplifies the same "beneficial synergistic effect" recognized in Demidem 1997. Similarly, as the Specification recognized the Demidem 1997 *in vitro* studies as meeting the claim requirement, we similarly recognize the *in vitro* studies reported in Demidem 1995 as doing so.

With regard to Patent Owner's assertion that a person of skill in the art would not have a reasonable expectation regarding achieving synergy with rituximab and CVP because "the Demidem authors did not test C, V, or P in their sensitization assay," PO Resp. 54–55 (citing Ex. 2020 ¶ 124), that argument is also unavailing. Demidem 1995, an abstract, describes investigating the effect of rituximab in combination with "drugs/toxins," without specifically identifying doxorubicin (Adriamycin). *See* Ex. 1078, 2 (identifying ricin, CDDP, and VP-16 results). For further support, Patent Owner looks to the study description in Demidem 1997. Demidem 1997 reports testing rituximab in combination with "various cytotoxic agents,"

identified as diphtheria toxin (DTX), ricin, cisplatinum diammine dichloride (CDDP), Adriamycin (ADR), i.e., doxorubicin, and VP16 etoposide. Ex. 1079, 2–3. Demidem 1997 explains that tumor cells treated with rituximab "were found to be more sensitive to all cytotoxic agents tested except VP-16 [etopside]." *Id*. at 6. Although the Demidem studies did not identify a component of CVP, that agent is a member of the category of drugs investigated, i.e., cytotoxic chemotherapy. Indeed, Demidem 1997 does not limit or otherwise exclude CVP from its conclusion relating to the combination of rituximab and chemotherapy, i.e., "treatment with combination of antibody and *chemotherapy* may improve overall anti-tumor response and prolongation of survival." *Id*. at 9 (emphasis added). Czuczman similarly described Demidem's conclusion as generally relating to "chemotherapy." Ex. 1011, 3. As a result, Patent Owner has not supported its assertion that a person of skill in the art would have considered Czuczman's characterization based upon the Demidem studies as demonstrating "synergy with chemotherapeutic agents" to be limited to synergy with doxorubicin chemotherapy, or to exclude synergy with other chemotherapy, such as CVP.

Based on the foregoing, we determine that Petitioner has established by a preponderance of the evidence that the combined teachings of Czuczman, Foon, and Dana would have suggested to those of ordinary skill in the art modifying Czuczman's method to substitute CVP for CHOP with a reasonable expectation that doing so would yield the inventions of claims 1–3. As this relates to an obviousness challenged, we next balance this determination with Patent Owner's asserted secondary considerations of nonobviousness.

Secondary considerations

Patent Owner asserts that the claimed invention yields unexpected beneficial results "with long-term outcomes, including median Time To disease Progression ("TTP") and, relatedly, Progression-Free Survival ("PFS"), in LG/F-NHL patients using R-CVP." PO Resp. 67. Specifically, Patent Owner asserts that "the surprising benefits of this therapy include a vast improvement in median TTP [time to progression] reported, e.g., to increase from 15 months (with CVP alone) to at least 32 months when patients were treated with the claimed method of using 375 mg/m^2 of rituximab during CVP therapy." *Id*. at 68–69 (citing Ex. 1005, 4; Ex. 1069, 120–21). For the asserted unexpected PFS results, Patent Owner refers to rituximab's current prescribing information as reporting a PFS of 1.4 years with CVP alone and 2.4 years with R-CVP. *Id*. at 69 (citing Ex. 2015, 24, and Table 5).

Patent Owner considers CVP as the closest prior art. Tr. 40:25–41:11. According to Patent Owner, the benefits of R-CVP as a treatment for LG/F-NHL were unexpected because "it was understood by those in the art that doxorubicin produced a particular beneficial effect with rituximab," as disclosed with Czuczman's R-CHOP regimen, but not with a CVP regimen that excluded doxorubicin. *Id*. at 69 (citing Ex. 2029 ¶ 58).

Petitioner asserts that Patent Owner has supported its assertion of unexpected results only with attorney arguments and not evidence. Reply 33 (citing *In re Soni*, 54 F.3d 746, 753 (Fed. Cir. 1995)). Further, Petitioner asserts that Patent Owner has not compared the challenged claims with the appropriate closest prior art. *Id*. According to Petitioner, the closest prior art is the "compelling result of combining rituximab with CHOP (which

contains all of the components of CVP),'' as report by Czuczman. *Id*. at 34. Petitioner asserts that a person of skill in the art "would have expected R-CVP to be much more effective than CVP alone" based upon the results reported by Czuczman for R-CHOP. *Id*. Further, Petitioner asserts that the "alleged 'benefits' of doxorubicin—rituximab sensitization or achievement of minimal tumor burden—also fails because neither is specific to doxorubicin." *Id*.

Based on the record as a whole, we agree with Petitioner that Patent Owner has not demonstrated that the benefits of combining rituximab and CVP in treating low grade or follicular NHL would have been unexpected when compared to the closest prior art. *See In re Baxter Travenol Labs.*, 952 F.2d at 392. In particular, we agree with Petitioner that a person of skill in the art would have considered the closest prior art regarding claims 1–3 to be Czuczman's chemoimmunotherapy comprising rituximab and CHOP. Czuczman describes the added benefit that rituximab provides when combined with CHOP over CHOP therapy alone, and further explains that the rationale for the combination included known rituximab "synergy with chemotherapeutic agents." Further, as discussed *supra*, none of the references cited by Patent Owner includes disclosures that a person of skill in the art would have considered Czuczman's rationale to apply only to CHOP or doxorubicin-containing agents. *See, e.g.* Exs. 1041, 1078, and 1079.

Accordingly, we determine that Patent Owner has not demonstrated that the inventions of claims 1–3 provide results that would have been unexpected when compared to the closest prior art. As a result, Patent Owner has not provided evidence of nonobviousness that outweighs our

determination that the combination of Czuczman, Foon, and Dana teaches or suggests each limitation of the challenged claims.

Based on the foregoing, we determine that Petitioner has established by a preponderance of the evidence that claims 1–3 are unpatentable under 35 U.S.C. § 103(a) as obvious over Czuczman, Foon, and Dana.

H. Obviousness over Czuczman, Foon, Dana, Link, and Piro

Petitioner asserts that claims 4–6 would have been obvious over Czuczman, IDEC 10-K/A, Foon, Dana, Link, and Piro. Pet. 54–61. As Petitioner has not shown that the IDEC 10-K/A is a prior art printed publication, we consider the obviousness challenge over Czuczman, Foon, Dana, Link, and Piro.

1. Link

Link is a journal abstract published in 1998 describing a phase II pilot study of the safety and efficacy of administering Rituxan (rituximab, IDEC-C2B8) in combination with CHOP chemotherapy to 31 patients with previously untreated intermediate or high grade NHL. Ex. 1010, 2 (Abstract 7). The dose of rituximab was 375 mg/m^2 on day 1 of each 21-day cycle, for 6 cycles. *Id*. According to Link, the study regimen "represents a tolerable therapy . . . and may offer higher response rates," than seen with conventional CHOP therapy alone. *Id.*

2. Piro

Piro is a journal abstract published in 1997 describing a phase II study involving administering Rituxan (rituximab) once weekly for 8 doses to treat patients with relapsed or refractory low grade or follicular NHL. Ex. 1004, 1, 3. Piro explains that an interim analysis suggest that an 8-week course of

Rituxan may be associated with a somewhat higher response rate than a 4-week course. *Id*. at 3.

3. Analysis

Petitioner asserts that the combination of Czuczman, Foon, and Dana teaches or suggests the method of treating low grade or follicular NHL comprising administering 375 mg/m^2 of rituximab during CVP therapy for the same reasons asserted for that combined art regarding claims 1–3. Pet. 54. Each of claims 4–6 additionally require that the rituximab dose is administered "once every 3 weeks for 8 doses." Ex. 1001, 25:8–26:16. For that dosing schedule, Petitioner relies on additional teachings from Czuczman, Link, and Piro.

In particular, Petitioner asserts that: (a) Czuczman teaches administering 375 mg/m^2 of rituximab for six cycles to treat low grade or follicular NHL, Pet. 54 (citing Ex. 1011, 3); (b) Link teaches administering 375 mg/m^2 of rituximab every three weeks for six doses to treat intermediate or high grade NHL, *id*. at 55 (citing Ex. 1010, 2); and Piro teaches administering 375 mg/m^2 of rituximab every week for eight doses, *id*. (citing Ex. 1004, 3). According to Petitioner and Dr. Lossos, those teachings would have provided a person of skill in the art motivation "to optimize the dosing regimens taught in Czuczman, Link and Piro by extending the rituximab dosing regimen of once every 3 weeks for 6 doses to once every 3 weeks for 8 doses," with a reasonable expectation of success. *Id*. at 59–61 (citing Ex. 1002 ¶ 118).

Patent Owner asserts, among other things, that Petitioner has not demonstrated that a person of ordinary skill in the art would have arrived at the dosing regimen required by claims 4–6 by combining the asserted

teachings of the cited references. PO Resp. 16. We agree with Patent Owner for at least the following reasons. To begin, none of the cited references teaches or suggests treating low grade or follicular NHL on a schedule of "once every 3 weeks." Petitioner relies on Link for that schedule, and as the proposed starting point for optimization. Pet. 55, 59. Link, however, is directed to treating a different type of NHL than that which is recited in the claimed methods. Petitioner has not explained, or referred us to a portion of Dr. Lossos' declaration explaining, why a skilled artisan would have found it appropriate to treat low grade NHL with Link's dosing schedule for treating intermediate or high grade NHL. Consequently, the basis for Petitioner's optimization argument is inadequately supported.

That result is unchanged by Petitioner's assertion in the Reply that Patent Owner argued in this proceeding that the '202 application described a dosing schedule of "once every three weeks" based upon the application disclosure for treating a lymphoma other than low grade or follicular NHL, i.e., mantle-cell lymphoma. Reply 35 (citing PO Resp. 65; Ex. 1034, 40). According to Petitioner, although that disclosure was insufficient to demonstrate that the inventors were in possession of the recited dosing regimen at the time of filing, such disclosures were sufficient to establish obviousness. *Id*. That conclusion would depend upon the arguments and evidence presented to establish that a person of skill in the art would have found it obvious to apply a dosing regimen disclosed for one disease for another. That argument and evidence is missing from the Petition and the record as a whole.

Thus, based on the record as a whole, we determine that Petitioner has not established by a preponderance of the evidence that claims 4–6 are unpatentable under 35 U.S.C. § 103(a) as obvious over Czuczman, Foon, Dana, Link, and Piro.

I. Obviousness over Czuczman, Foon, Dana, Link, Piro, and the '137 Patent

Petitioner asserts that claims 3 and 6 would have been obvious over Czuczman, IDEC 10-K/A, Foon, Dana, Link, Piro, and the '137 Patent. Pet. 62–63. As Petitioner has not shown that IDEC 10-K/A is a prior art printed publication, we consider the obviousness challenge over Czuczman, Foon, Dana, Link, Piro, and the '137 Patent.

Regarding claim 3, Petitioner relies on the same arguments regarding the combination of Czuczman, Foon, and Dana asserted for the challenge of claim 3 discussed above in Section II. G. Pet. 62. Petitioner explains that the '137 patent is added in this ground only for its disclosure of the sequence of rituximab. *Id*. Petitioner does not explain how the teachings of Link and Piro support its challenge of claim 3. Therefore, we understand this challenge of claim 3 as being over Czuczman, Foon, Dana, and the '137 Patent. Patent Owner does not raise separate arguments for this ground.

Based on the record as a whole, we determine that Petitioner has established by a preponderance of the evidence that Czuczman, Foon, Dana, and the '137 patent teach or suggest each limitation of the invention of claim 3 for the same reasons discussed in Section II. G. Moreover, insofar as Patent Owner intended to assert its secondary considerations to this Czuczman ground, *see* PO Resp. 67, we find that Patent Owner has not demonstrated that the invention of claim 3 provides results that would have

been unexpected when compared to the closest prior art for the same reasons discussed in Section II. G.

Regarding claim 6, Petitioner relies on its same arguments regarding the combination of Czuczman, Foon, Dana, Link, and Piro asserted regarding the challenge of claim 6 discussed above in Section II. H. Pet. 62. Petitioner explains that the '137 patent is added in this ground only for its disclosure of the sequence of rituximab. *Id*. Petitioner does not rely on the '137 patent in a manner that addresses or cures the deficiencies we discussed regarding the dosing schedule for rituximab required by claim 6.

Accordingly, based on the record as a whole, we determine that Petitioner has not established by a preponderance of the evidence that claim 6 is unpatentable over Czuczman, Foon, Dana, Link, Piro, and the '137 patent for the same reasons discussed in Section II. H.

IV. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has shown by a preponderance of the evidence that claims 1–6 are unpatentable.

ORDER

Accordingly, it is hereby:

ORDERED that claims 4–6 are unpatentable under 35 U.S.C. § 102(b) as anticipated by Marcus;

FURTHER ORDERED that claim 6 is unpatentable under 35 U.S.C. § 103(a) as obvious over Marcus and the ’137 patent;

FURTHER ORDERED that claims 1–3 are unpatentable under 35 U.S.C. § 103(a) as obvious over Czuczman, Foon, and Dana;

FURTHER ORDERED that claim 3 is unpatentable under 35 U.S.C. § 103(a) as obvious over Czuczman, Foon, Dana, and the ’137 patent; and

FURTHER ORDERED that because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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Patent 9,296,821 B2

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