UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

BIOGEN, INC.,
Patent Owner.

Inter Partes Review No. IPR2018-00186
Patent 9,296,821 B2
Issued: March 29, 2016
Filed: June 15, 2012

Title: COMBINATION THERAPIES FOR B-CELL LYMPHOMAS COMPRISING ADMINISTRATION OF ANTI-CD20 ANTIBODIES

PETITION FOR *INTER PARTES* REVIEW

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES

OTHER AUTHORITIES

LIST OF EXHIBITS

Exhibit	Description
1001	Antonio J. Grillo-Lopez, U.S. Patent No. 9,296,821 B2 "Combination Therapies for B-Cell Lymphomas Comprising Administration of Anti-CD20 Antibodies" (issued March 29, 2016) ("the '821 patent")
1002	Declaration of Howard Ozer, M.D., Ph.D. in Support of Petition for *Inter Partes* Review
1003	Steward et al., "Maintenance Chlorambucil After CVP in the Management of Advanced Stage, Low-Grade Histologic Type Non-Hodgkin's Lymphoma," Cancer, 61(3):441-447 (1988) ("Steward")
1004	Czuczman et al., "IDEC-C2B8 and CHOP Chemoimmunotherapy of Low-Grade Lymphoma," Blood, 86(10 Supp. 1):55a (1995) ("Czuczman")
1005	Maloney et al., "IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients with Relapsed Low-Grade Non-Hodgkin's Lymphoma," Blood, 90(6):2188-2195 (1997) ("Maloney (Sept. 1997)")
1006	Kenneth A. Foon & Richard I. Fisher, "Lymphomas" in Williams Hematology 5th Ed. (Ernest Beutler et al., eds.) 1076-1096 (1995) ("Foon")
1007	Dana et al., "Long-Term Follow-Up of Patients with Low-Grade Malignant Lymphomas Treated with Doxorubicin-Based Chemotherapy or Chemoimmunotherapy," J. Clinical Oncology 11(4):644-651 (1993) ("Dana")
1008	Marcus et al., "CVP Chemotherapy Plus Rituximab Compared with CVP as First-Line Treatment for Advanced Follicular Lymphoma," Blood, 105(4):1417-1423 (2005) ("Marcus")
1009	Lauren C. Pinter-Brown and Dennis A. Casciato, "Hodgkin and Non-Hodgkin Lymphoma," in Manual of Clinical Oncology 6th Ed. (Dennis A. Casciato, ed.) 431-470 (2009) ("Pinter-Brown")

1010	Anderson et al., U.S. Patent No. 5,736,137 "Therapeutic Application of Chimeric and Radiolabeled Antibodies to Human B Lymphocyte Restricted Differentiation Antigen for Treatment of B Cell Lymphoma" (issued April 7, 1998) ("the '137 patent")
1011	Rituxan™ (rituximab) labeling (Nov. 1997) ("Rituxan™ label")
1012	Physicians' Desk Reference® (53rd ed. 1999) (excerpted), "Rituxan™ (Rituximab)" ("PDR label")
1013	Maloney et al., "IDEC-C2B8: Results of a Phase I Multiple-Dose Trial in Patients with Relapsed Non-Hodgkin's Lymphoma," J. Clinical Oncology, 15(10):3266-3274 (1997) ("Maloney (Oct. 1997)")
1014	Arthur T. Skarin & David M. Dorfman, "Non-Hodgkin's Lymphomas: Current Classification and Management," CA Cancer J. Clinicians, 47(6):351-372 (1997) ("Skarin")
1015	W. Hiddemann, "Non-Hodgkin's Lymphoma—Current Status of Therapy and Future Perspectives," Eur. J. Cancer, 31A:2141-2145 (1995) ("Hiddemann")
1016	Sriskandan et al., "Aggressive Management of Doxorubicin-Induced Cardiomyopathy Associated with 'Low" Doses of Doxorubicin," Postgraduate Med. J., 70(828):759-761 (1994) ("Sriskandan")
1017	Bishop et al., "A Randomized Trial of High Dose Cyclophosphamide, Vincristine, and Prednisone Plus or Minus Doxorubicin (CVP Versus CAVP) with Long-Term Follow-up in Advanced Non-Hodgkin's Lymphoma," Leukemia, 1(6):508-513 (1987) ("Bishop")
1018	McLaughlin et al., "Rituximab Chimeric Anti-CD Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program," J. Clinical Oncology, 16(8):2825-2833 (1998) ("McLaughlin")
1019	Pierre Feugier, "A Review of Rituximab, the First Anti-CD20 Monoclonal Antibody Used in the Treatment of B Non-Hodgkin's Lymphomas," Future Oncology, 11(9):1327-1342 (2015) ("Feugier")

1020	Demidem et al., "Chimeric Anti-CD20 (IDEC-C2B8) Monoclonal Antibody Sensitizes a B Cell Lymphoma Cell Line to Cell Killing by Cytotoxic Drugs," Cancer Biotherapy & Radiopharmaceuticals, 12(3):177-186 (1997) ("Demidem")
1021	Declaration of Sylvia D. Hall-Ellis, Ph.D.
1022	Institution of *Inter Partes* Review, *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01095 (U.S. Patent No. 9,296,821) Paper 12 (PTAB)
1023	Petition for *Inter Partes* Review, *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01095 (U.S. Patent No. 9,296,821) Paper 2 (PTAB)
1024	U.S. Application No. 09/372,202 (dated August 11, 1999)
1025	U.S. Application No. 13/524,896, Non-Final Office Action (dated December 31, 2012)
1026	U.S. Application No. 13/524,896, Amendment and Response (dated March 28, 2013)
1027	U.S. Application No. 13/524,896, Amendment and Response (dated April 25, 2014)
1028	U.S. Application No. 13/524,896, Final Office Rejection (dated September 16, 2014)
1029	U.S. Application No. 13/524,896, Amendment and Response (dated September 18, 2015)
1030	U.S. Application No. 13/524,896, Applicant-Initiated Interview Summary and Notice of Issuance (dated February 26, 2016)
1031	U.S. Provisional Application No. 60/096,180 (filed August 11, 1998)
1032	Michael J. Campbell & John E. Niederhuber, "B-Lymphocyte Responses," Clinical Oncology, Abeloff et al., Eds. (1995), 100-126 ("Campbell")
1033	Michael L. Grossbard and Pratik S. Multani, "Clinical Status and Optimal Use of Rituximab for B-Cell Lymphomas," Psychiatric Times, (December 1, 1998) ("Grossbard")

I. INTRODUCTION

Petitioner Pfizer, Inc. requests *inter partes* review and cancellation of claims 1-6 of U.S. Patent No. 9,296,821 B2 ("the '821 patent"). These claims are directed to methods of treating low-grade or follicular B-cell non-Hodgkin's lymphoma ("NHL"), which is a type of cancer. Generally speaking, the claims recite [1] a method of treating low-grade or follicular NHL with "CVP" chemotherapy[1]; along with [2] 375 mg/m^2 of the monoclonal antibody rituximab [3] every three weeks for eight cycles (for some claims) [4] with a beneficial synergistic effect (for some claims). As demonstrated below, the claimed invention would have been obvious to a person of ordinary skill in the art ("POSA") as of the earliest filing date to which the claims are entitled—June 15, 2012, for claims 4-6 and August 11, 1999, for claims 1-3—in light of references that are prior art under 35 U.S.C. § 102(b) as well as § 102(a). *See* Ex. 1022, 11-12 (related institution decision finding that claims 4-6 are entitled to a priority date no earlier than June 15, 2012).

Even assuming a priority date of August 11, 1999, for all the claims (contrary to the finding of the Board in IPR2017-01095), claims 1-6 would have also been

[1] CVP is an acronym used by skilled artisans in the field to describe a chemotherapy regimen that consists of cyclophosphamide, vincristine (or Oncovin®), and prednisone (or prednisolone). Ex. 1002 ¶ 1 n.1.

obvious as of that date. The state of the art as of August 1999 was to use chemotherapy, with CVP being a preferred therapy, as a first-line treatment for patients with low-grade or follicular NHL at its standard 21-day cycle for six to ten cycles. Ex. 1003, Steward at 7.

By August 1999, the prior art had also disclosed the monoclonal antibody rituximab as a treatment that, as shown below, reasonably would have been expected to achieve improved and even synergistic results if added to CVP therapy. By 1997, the U.S. Food and Drug Administration ("FDA") had approved rituximab at a "recommended" dosing of 375 mg/m^2 once a week for four weeks for the treatment of low-grade B-cell lymphomas. Ex. 1011, Rituxan™ label at 2; Ex. 1012, PDR label at 8. Rituximab binds to the CD20 antigen that is expressed in the B cells of over 90 percent of lymphoma patients, and induces the death of those cells. Ex. 1011, Rituxan™ label at 1; Ex. 1012, PDR label at 6; Ex. 1005, Maloney (Sept.) 1997 at 6-7, 11-12 (showing that weekly doses of 375 mg/m^2 are safe and effective); Ex. 1002 ¶ 52.

It would have been obvious to combine 375 mg/m^2 of rituximab to CVP chemotherapy regimens to treat low-grade NHL. The prior art disclosed numerous motivations to combine these therapies, including rituximab's "single agent efficacy, non cross-resistant mechanism of action, synergy with chemotherapeutic agents and non-overlapping toxicities." Ex. 1004, Czuczman at 11; *see also* Ex. 1013, Maloney

(Oct.) 1997 at 4 (noting rituximab makes cancerous cells more sensitive to the effects of chemotherapy). Maloney (Sept.) 1997—which showed that 375 mg/m^2 of rituximab was safe and effective in treating low-grade NHL patients—suggested that "[a]dditional areas that should be investigated using this new agent include (1) extended and repeated dosing regimens, [and] (2) combination with or after standard chemotherapy[.]" Ex. 1005, 12.

Therefore, as explained in the declaration of Dr. Howard Ozer, claims 1-6 of the '821 patent would have been obvious to a POSA as of August 1999 over the combined teachings of the Steward, Czuczman, and Maloney (Sept.) 1997 references. Ex. 1002 ¶¶ 66-90. Additionally, claims 1-3 are independently obvious over Czuczman in light of the Foon and Dana prior art, which similarly taught CVP was a preferred treatment for low-grade NHL. Ex. 1002 ¶¶ 91-92. A panel of this Board has instituted trial on claims 1-3 in a related proceeding brought by Celltrion (Case IPR2017-01095) on the basis of this combination of prior art. Ex. 1022, 24. (The panel did not institute trial on claims 4-6 based on this combination.)

As discussed, a panel of this Board already found that the priority date for claims 4-6 is over a decade later, June 15, 2012. With that priority date, claims 4-6 would have been anticipated by the 2005 Marcus reference or, at minimum, rendered obvious over Marcus and other prior art. Marcus disclosed the exact method claimed by the '821 patent—the use of 375 mg/m^2 of rituximab in combination with CVP

for low-grade NHL patients every three weeks for eight cycles with beneficial results. Ex. 1008, 9-10.

To be sure, claim 4 (like claim 1) recites a "beneficial synergistic effect in the patient," but this is merely a "statement of the intended result of administering [the claimed 375 mg/m^2] amount[]" of rituximab and thus "does not change [that] amount[] or otherwise limit the claim." *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001); *see also* Ex. 1002 ¶ 31. Even if the synergy requirement were limiting, a POSA would have also reasonably expected such synergistic results in light of Marcus's teaching that "[d]ata from in vitro studies suggest that rituximab can sensitize lymphoma cell lines to chemotherapy," and "a synergistic effect between rituximab and various cytotoxic agents has been demonstrated." Ex. 1008, 10. Therefore, at minimum these claims would have been obvious over Marcus in view of Czuczman and the *Manual of Clinical Oncology* ("Pinter-Brown"), which collectively would have also given a POSA a reasonable expectation of synergy when combining 375 mg/m^2 of rituximab and CVP to treat low-grade NHL. Ex. 1002 ¶¶ 97-99.

In sum, all the claims of the '821 patent should be cancelled as obvious.

II. MANDATORY NOTICES

Pursuant to 37 C.F.R. § 42.8(b), Petitioner states as follows:

1. ***Real parties-in-interest.*** The real party in interest is Petitioner Pfizer, Inc. ("Pfizer" or "Petitioner"). No other parties exercised or could have exercised control over this Petition; no other parties funded or directed this Petition. *See* Trial Practice Guide, 77 Fed. Reg. 48,759-60.

2. ***Related matters.*** Celltrion, Inc. ("Celltrion") has filed a petition challenging claims 1-6 of the '821 patent. The Board instituted proceedings on claims 1-3 (based on Ground II presented in this petition) and 5-6 (based on Ground IV presented in this petition). *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01095, Paper 12 at 34 (PTAB Oct. 6, 2017). Celltrion has filed a request for rehearing on its challenge to claim 4. The present petition presents additional combinations of prior art and additional claim construction arguments not considered by the Board in IPR2017-01095.

The '821 patent is a division of U.S. Application No. 11/840,956 ("the '956 application"), which issued as U.S. Patent No. 8,329,172 ("the '172 patent"). The '956 application is a continuation of U.S. Application No. 10/196,732, now abandoned, which is a continuation of U.S. Application No. 09/372,202 ("the '202 application"), which was filed August 11, 1999 and issued as U.S. Patent No. 6,455,043 ("the '043 patent").

The '172 patent was previously challenged by Petitioner Boehringer in *Boehringer Ingelheim International GmbH v. Biogen Idec, Inc.*, No. IPR2015-

00415 and Petitioner Celltrion in *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01093. The Board denied institution in case IPR2015-00415 on July 13, 2015 (Paper 14), and denied institution in case IPR2017-01093 on October 6, 2017 (Paper 12). Petitioner here also filed a petition for *inter partes* review challenging the '172 patent in case *Pfizer, Inc. v. Biogen, Inc.*, IPR2017-01166. The Board recently denied institution in that case as well. The '172 patent claims methods of treating low-grade NHL using rituximab as maintenance therapy following CVP, whereas the '821 patent claims methods of treating low-grade NHL using rituximab and CVP as front-line therapy.

Petitioner has concurrently filed a petition challenging U.S. Patent No. 9,504,744 B2, which also claims methods of using rituximab to treat NHL, and which is owned by Patent Owner here. IPR2018-00231. That petition relies on the same subject-matter expert (Dr. Ozer) as the present petition.

3. ***Lead and back-up counsel.*** Petition identifies the following:

- *Lead counsel*: Jovial Wong (Reg. No. 60,115)
- *Back-up counsel*: Charles B. Klein*
- *Back-up counsel*: Eimeric Reig-Plessis*

* Back-up counsel to seek *pro hac vice* admission.

4. ***Service information.*** Petitioner identifies the following:

- *Email address*: rituximabIPR@winston.com

- *Mailing address*: WINSTON & STRAWN LLP
  1700 K Street NW
  Washington, DC 20006
- *Telephone number*: (202) 282-5000
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Please address all correspondence to lead counsel at the address shown above. Petitioner consents to electronic service at the above listed email address.

III. REQUIREMENTS FOR REVIEW

Pursuant to 37 C.F.R. § 42.104, Petitioner states as follows:

a. Grounds for standing. Petitioner certifies that (1) the ’821 patent is available for *inter partes* review; and (2) Petitioner is not barred or estopped from requesting review of any claim of the ’821 patent on the grounds identified in this Petition. The required fee is paid through the Patent Review Processing System. The Office is authorized to charge fee deficiencies and credit overpayments to Deposit Acct. No. 50-1814.

b. Identification of challenge. Pursuant to 37 C.F.R. §§ 42.104(b) and 42.22(a)(1), Petitioner requests review and cancellation of claims 1-6 of the ’821 patent pursuant to the following statement of the precise relief requested:

Ground	Claims	Basis	Reference(s)
I	1-6	§ 103	Steward (Ex. 1003), Czuczman (Ex. 1004), and Maloney (Sept.) 1997 (Ex. 1005)
II	1-3	§ 103	Czuczman (Ex. 1004), Foon (Ex. 1006), and Dana (Ex. 1007)
III	4-6	§ 102	Marcus (Ex. 1008)
IV	4-6	§ 103	Marcus (Ex. 1008), Czuczman (Ex. 1004), and Pinter-Brown (Ex. 1009)

Pursuant to 37 C.F.R. § 42.22(a)(2), Petitioner sets forth a full statement of the reasons for the relief requested below in Sections IX and X.

IV. LEVEL OF ORDINARY SKILL IN THE ART

The application that became the '821 patent was filed on June 15, 2012. This application claims priority to U.S. Provisional Application No. 09/372,202, which was filed on August 11, 1999.[2] Without conceding that either priority date is valid, Dr. Ozer explains that the level of skill in the art would not materially change

[2] As suggested above and explained further below, although Patent Owner filed a provisional application on August 11, 1998, patentee did not rely on that application during prosecution, and the Examiner found that this provisional application did not adequately disclose the claims that were eventually allowed. *See infra* Part VI.B.

regardless of which priority date is used to assess prior art, except that a POSA as of 2012 would have had additional prior art references to consider.

In light of the specification, the prosecution history, and the state of the art, a POSA for purposes of the '821 patent would include a practicing oncologist with at least an M.D. degree and several years of experience treating patients with NHL and/or researching treatments for NHL, including with chemotherapeutic drugs. Ex. 1002 ¶ 15.

V. THE PRIOR ART

In summarizing the state of the art as of June 2012 (and August 1999), Petitioner cites additional references beyond "prior art presented as the basis for obviousness," which "legitimately serve to document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness." *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015).

A. Since the 1980s, continuing through August 1999, a three-week cycle of CVP for six to ten cycles was a preferred therapy for low-grade or follicular NHL, but better therapies were needed.

NHL is a cancer that targets the body's lymphatic system. Ex. 1002 ¶ 41. NHL is a type of B-cell lymphoma characterized by the uncontrollable growth of the body's B-cells. *Id.* B-cells are the body's white blood cells that distribute antibodies in the system when they grow into mature cells. They are also referred to as B

lymphocytes. *Id.* ¶ 42. NHL manifests in different ways in different patients: "[N]on-Hodgkin's lymphomas constitute a heterogenous [*sic*] group of neoplasms of the lymphoid system that include distinct entities defined by clinical histologic, immunologic, molecular, and genetic characteristics." Ex. 1014, Skarin at 1; *see* Ex. 1002 ¶ 44. One of the central determining factors for a patient's prognosis was (and remains) his or her grade of lymphoma: low-, intermediate-, or high-grade NHL. Ex. 1002 ¶ 45. Low-grade lymphomas, unlike intermediate- and high-grade lymphomas, grow more slowly. *Id.* Intermediate- and high-grade NHL patients were considered to have an aggressive form of NHL marked by rapidly growing tumorous cells. But unlike low-grade patients, they were frequently curable. Ex. 1015, Hiddemann at 2-3; Ex. 1014, Skarin at 3-5.

By 1999, chemotherapy was the preferred first-line treatment for NHL. Ex. 1002 ¶ 46. As with other cancers, chemotherapy was a standard therapy aimed at stopping the division (and thus growth) of cancerous cells. Chemotherapy affects cellular metabolism at the level of DNA, cell division, or RNA synthesis, or it interferes with epigenetics. In short, chemotherapy interferes with the process of cell division and growth in various ways, and thus affects all cells in the body but particularly cancer cells, which are prone to divide and grow at a rate faster than non-malignant cells. *Id.*

The two main combinations of chemotherapeutic drugs for treating NHL as of August 1999 were commonly abbreviated as "CVP" and "CHOP." *Id.* ¶ 47. "CVP" consists of cyclophosphamide, vincristine, and prednisone. *Id.* Because vincristine is also known as Oncovin®, CVP was also sometimes referred to as "COP." *Id.* CHOP contains the same three drugs as CVP, but additionally combines a fourth drug called hydroxydaunorubicin (the "H" in CHOP), which is also called doxorubicin. *Id.* ¶ 48. CHOP was generally considered a more potent therapy than CVP. *Id.* Due to the addition of doxorubicin, it had better efficacy against more aggressive forms of NHL (i.e., intermediate- and high-grade NHL), but was also significantly more toxic. *Id.*; *see also, e.g.*, Ex. 1016, Sriskandan at 3 (discussing the "relationship between doxorubicin and the incidence of symptomatic cardiac failure," even at low doses).

As of August 1999 (and, for that matter, today), CHOP was the preferred treatment for intermediate- and high-grade NHL. Ex. 1002 ¶ 49. "In low-grade lymphomas," however, the main "therapeutic intervention" at the time (and today) "consist[ed] preferentially of chemotherapy of moderate intensity such as cyclophosphamide, vincristine and prednisone"—i.e., CVP. Ex. 1015, Hiddemann at 1. Indeed, as far back as 1988, "combination chemotherapy (predominantly CVP)" was known to have the "greatest and complete response rates" for low-grade NHL. Ex. 1003, Steward at 10. Steward studied "three-weekly" courses of CVP

given until "two courses beyond complete remission with a minimum of six and a maximum of ten courses." *Id.* at 7. CVP in a three-weekly course for six to ten cycles, and more often six to eight cycles, was one of the preferred therapies for treating low-grade NHL as of August 1999. Ex. 1002 ¶¶ 51, 57.

However, "[d]espite these high response rates" to initial chemotherapy, low-grade NHL was understood as being characterized by "a pattern of continuing relapse with RFS [i.e., relapse-free survival] of only 2 to 3 years" following chemotherapy. Ex. 1003, Steward at 10. At first, oncologists attempted to address the problem of relapses with "more aggressive regimens of combination chemotherapy including . . . CHOP," but "[u]nfortunately these studies have not produced obvious improvements of the percentage or duration of responses or survival, and often have resulted in more toxicity." *Id.*

Researchers similarly found in 1987 that "CVP was as effective" as CHOP for low-grade NHL, and "doxorubicin does not enhance the activity of the CVP regimen against lymphomas other than diffuse large cell [lymphoma]," a type of intermediate-grade NHL. Ex. 1017, Bishop at 6. The Dana reference confirmed again in 1993 that "[d]oxorubicin-containing treatment [i.e., CHOP] did not prolong the overall median survival of low-grade lymphoma patients compared with results with less-aggressive programs," i.e., CVP. Ex. 1007, Dana at 7. And Foon in 1995 similarly taught that both CVP and CHOP are effective in low-grade NHL patients,

but that "there is no evidence that [CHOP] treatment prolongs survival" compared to CVP. Ex. 1006, Foon at 41-42.

Thus, CVP remained a preferred first-line treatment for low-grade NHL, despite the problem of relapses following the initial response to chemotherapy (a problem that persists to this day). Ex. 1002 ¶¶ 51, 57-58. Indeed, Steward noted that "[i]mprovements in the survival of patients with advanced-stage low-grade NHL probably will require new approaches to the initial induction of remission," particularly for patients with poor prognostic factors, but it is "just such patients who would tolerate the toxicity of more aggressive regimens badly." Ex. 1003, 11.

B. In November 1997, rituximab became a new therapy for treating NHL with minimal toxicity, and showed signs of synergy with chemotherapeutic drugs.

In November 1997, FDA approved rituximab under the brand name Rituxan™ for the treatment of relapsed or refractory low-grade or follicular B-cell NHL. Ex. 1011, Rituxan™ Label at 1; Ex. 1012, PDR label at 6; Ex. 1002 ¶ 52. Rituximab, also known by its code name "IDEC-C2B8," is an antibody that binds to "CD20," a protein that is only expressed on the surface of B-cells. Ex. 1011, 1; Ex. 1012, 6; Ex. 1018, McLaughlin at 3. By targeting this specific protein, rituximab can selectively activate the immune system to kill only B-cells, without harming other cells in the body. Ex. 1002 ¶ 52.

As of August 1999, rituximab was the only anti-CD20 agent approved by FDA. Ex. 1002 ¶ 53. It is widely recognized as "the first anti-CD20 monoclonal antibody used in the treatment of B non-Hodgkin's lymphomas," and "the first targeted therapy used in B-cell malignancies." Ex. 1019, Feugier at 1. Rituximab was approved at a single "recommended" dosing regimen of 375 mg/m^2 in four weekly doses. Ex. 1011, Rituxan™ Label at 2; Ex. 1012, PDR label at 8.

In September 1997, Maloney reported on a clinical trial testing 375 mg/m^2 of rituximab in four weekly doses in relapsed low-grade NHL patients, a study that demonstrated "clinical responses with no dose-limiting toxicity." Ex. 1005, 6. Maloney (Sept.) 1997 confirmed that rituximab "efficiently kills CD20$^+$ cells in vitro by augmented complement-mediated lysis and participates in antibody-dependent cell-mediated cytotoxicity (ADCC)," and in some cases "inhibits proliferation and directly induces apoptosis." *Id.* at 6-7. This study confirmed to a POSA that weekly doses of 375 mg/m^2 of rituximab were safe and effective in treating low-grade NHL. Ex. 1002 ¶ 62. It showed no dose-limiting toxicity. Ex. 1005, 6 ("single doses up to 500 mg/m^2 and 4 weekly doses of 375 mg/m^2 showed clinical responses with no dose-limiting toxicity").

Researchers concluded that rituximab should be combined with chemotherapy. "By virtue of the modest toxicities of this agent [rituximab], which do not overlap with the toxicities of standard chemotherapy"—and because

rituximab has a mechanism of action that is different than and complementary to that of chemotherapies like CVP—rituximab "lends itself to integration with chemotherapy programs." Ex. 1018, McLaughlin at 9; Ex. 1002 ¶¶ 54-55.

In 1995, Czuczman reported results from a trial with rituximab in combination with CHOP chemotherapy in relapsed low-grade NHL patients. The authors wrote that "[t]he rationale for combination of IDEC-C2B8 [rituximab] with CHOP includes: single agent efficacy, non cross-resistant mechanism of action, synergy with chemotherapeutic agents and non-overlapping toxicities." Ex. 1004, 11. Rituximab was given at a dose of 375 mg/m^2 on weeks 1 (two infusions), 7, 13, 20, and 21, for a total of six infusions. *Id.* The initial response rate was 100%—with 11 complete responses and 3 partial responses. *Id.*

In October 1997, Maloney taught that rituximab made cancerous B-cells more vulnerable to the effects of chemotherapy—specifically, that rituximab "increases sensitivity to the cytotoxic effect of chemotherapy/toxins in some resistant human lymphoma cell lines"—suggesting a rationale to combine the drugs. Ex. 1013, Maloney (Oct.) 1997 at 4; *see also* Ex. 1020, Demidem at 7-8 (rituximab makes B-cells more sensitive to chemotherapy and rituximab-induced apoptosis may be "complemented and completed by the cytotoxic drugs"). Maloney (Sept.) 1997 suggested that "[a]dditional areas that should be investigated using this new agent include (1) extended and repeated dosing regimens, [and] (2) combination with or

after standard chemotherapy"—such as CVP. Ex. 1005, 6-7, 12. And in 1998, another prior art reference taught that "[i]n vitro data suggesting synergy of rituximab with conventional chemotherapy represent the most exciting potential for this agent." Ex. 1033, Grossbard at 1.

By 1999, in sum, it was widely recognized that rituximab could be used in combination with a variety of chemotherapeutic drugs.

C. In 2005, Marcus showed rituximab in combination with CVP in eight three-week cycles had beneficial results for low-grade NHL patients.

In 2005, Marcus studied rituximab in combination with CVP in low-grade NHL patients. Marcus noted that CVP was one of only two standard therapies for low-grade NHL. Ex. 1008, 9. Marcus further noted that rituximab "has been shown to be effective in the treatment of follicular lymphoma" through several mechanisms of action at weekly doses of 375 mg/m^2. *Id.* at 9-10. Marcus then disclosed that "[d]ata from in vitro studies suggest that rituximab can sensitize lymphoma cell lines to chemotherapy," and that "a synergistic effect between rituximab and various cytotoxic agents has been demonstrated." *Id.* at 10.

"In view of these results," Marcus evaluated the combination of rituximab and CVP ("R-CVP") in low-grade NHL patients and compared the results to CVP alone. *Id.* The R-CVP regimen comprised 375 mg/m^2 of rituximab given with CVP on "day 1" of each three-week cycle, for a maximum of eight cycles. *Id.* Eighty-five

percent (85%) of the patients in the R-CVP group received all eight cycles of treatment. *Id.* at 11. Eighty-one percent (81%) in this group responded to the therapy, with 41% achieving a complete response, compared to 62% and 21% in the CVP arm, respectively. The median time to disease progression was 32 months in the R-CVP group compared to 15 months in the CVP group. *Id.* The number of adverse effects were comparable across both groups. *Id.* at 13. The authors summarized: "In this study the addition of rituximab to CVP demonstrated major improvements in all clinical end points with minimal additional side effects. R-CVP is a highly effective, short, and very low-toxicity regimen that *may now be considered as a new standard regimen* for the treatment of previously untreated patients with follicular NHL." *Id.* at 14 (emphasis added).

D. By June 2012, other references confirmed the expectation of synergy when combining rituximab with CVP.

Additional prior-art references confirmed by June 2012 what was already reasonably expected in light of Czuczman and Marcus: that rituximab and CVP in combination would likely result in synergy. In 2009, the textbook *Manual of Clinical Oncology* ("Pinter-Brown") disclosed that CVP was a standard regimen for treating low-grade NHL. Ex. 1009, 46. Pinter-Brown also disclosed that rituximab was "the first-line therapy [for low-grade NHL] when combined with CVP." *Id.* And on the same page, Pinter-Brown disclosed that "[c]ombinations of rituximab

with a variety of chemotherapy regimens are feasible and are believed to be synergistic." *Id.*

VI. PATENT CLAIMS, SPECIFICATION, AND FILE HISTORY

A. The '821 patent

The '821 patent includes six claims, all of which are independent claims. Claims 1, 4, and 6 of the '821 patent are representative of the claims and describe the following:

> 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.

> 6. A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL) comprising administering to a patient 375 mg/m^2 of a chimeric anti-CD20 antibody once every 3 weeks for 8 doses during a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy), wherein the chimeric anti-CD20 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.

B. The '821 specification and prosecution history

The '821 patent issued on March 29, 2016, from U.S. Application No. 13/524,896. The '896 application was filed on June 15, 2012, but claimed priority, through a series of continuation applications, to U.S. Application No. 09/372,202 ("the '202 application"), which in turn was filed on August 11, 1999. Ex. 1024. The '202 application claimed priority to U.S. Provisional Application No. 60/096,180, which was filed on August 11, 1998. Ex. 1031.

Regarding the provisional '180 application filed in 1998, the Examiner concluded that "[t]he claimed inventions are not disclosed in parent application 60/096180," and "[t]herefore, regarding the application of prior art, the instant application is not entitled to priority to said application." Ex. 1025, 7. The Applicants never traversed that finding. Indeed, throughout the remainder of the

prosecution, Applicants solely relied on the '202 application to support the amendments to their application. *See, e.g.*, Ex. 1029, 4. A panel of this Board agreed in IPR2017-01095 that claims 1-3 are entitled to a priority date no earlier than August 11, 1999. Ex. 1022, 11; *see also* Ex. 1002 ¶¶ 35-36.

However, because the '202 application from 1999 does not include an adequate written description to support claims 4-6 of the '821 patent, these claims are entitled to a priority date no earlier than June 15, 2012. These claims all require a particular dosing and frequency: 375 mg/m^2 of rituximab in combination with CVP every three weeks for a total of eight cycles.

Claim 4—which is representative of claims 4-6—originated from claim 6 of the '896 application filed in 2012. As originally filed, claim 6 of the '896 application was as follows:

> 6. (New) A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL) comprising administering to a patient a therapeutically effective amount of rituximab in combination with a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy).

Ex. 1026, 3. The claim was later amended in 2014 to specify the use of rituximab "during" a chemotherapeutic regimen; to add the limitation "wherein the method provides a beneficial synergistic effect in the patient"; and to specify the 375 mg/m^2

dosage amount and frequency (every three weeks for eight cycles) of rituximab. *See, e.g.*, Ex. 1027, 1-3.

Throughout prosecution, Applicants argued that the '202 application filed in 1999 "discloses the presently claimed invention." *E.g.*, *id.* at 5. With respect to the dosing and frequency of rituximab administration, for example, Applicants relied on the following passages from the '202 specification: 22:4, 28:14, and 35:15 for the rituximab dose, and 25:16-17, 28:2, 36:2 and 36:14 for the frequency. *Id.* The Examiner repeatedly rejected Applicants' assertions, finding that nothing in the '202 application disclosed combining rituximab with CVP, using this combination in low-grade NHL patients, the expectation of synergy, or the thrice-weekly dosing for eight cycles. With respect to the dosing and frequency, the Examiner noted that the specification did not disclose 375 mg/m^2 rituximab in combination with CVP every three weeks for eight cycles. Rather, the cited passages disclosed eight *weekly* doses of rituximab, *or* CVP every three weeks, *or* CHOP chemotherapy for six cycles—but not 375 mg/m^2 of rituximab every three weeks for eight cycles. Ex. 1028, 3-4.

A panel of this Board agreed in the institution context. In IPR2017-01095, the panel concluded that "Patent Owner has not provided evidence demonstrating that the claimed dosing regimen for rituximab once every three weeks for eight doses was in the possession of the inventors." Ex. 1022, 12. Thus, "the '202 application does not provide written description support for" claims 4-6. *Id.* Claims 4-6 in that

related proceeding were entitled to a priority date of no earlier than June 15, 2012, as they are here.[3] Ex. 1002 ¶¶ 37-39.

VII. CLAIM CONSTRUCTION

The terms of the '821 patent should be given their broadest reasonable interpretation, which in this case is their plain and ordinary meaning. "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification. The plain meaning of a term means the ordinary and customary meaning given to the term by those of ordinary skill in the art at the time of the invention." MPEP § 2111.01. "[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc).

A. "beneficial synergistic effect"

The construction of the term "beneficial synergistic effect" is at issue in the IPR2017-01095 proceeding. Petitioner Celltrion Inc. argues that this term means "an improvement in clinical outcome." Ex. 1022, 5. Patent Owner argues that the

[3] The Examiner had eventually allowed the claims after an interview with Applicants, but provided no statement of reasons for the allowance. Ex. 1030.

term requires "an effect better than the additive effects of rituximab and CVP administered alone." *Id.* at 6. The Board made an initial determination that "beneficial synergistic effect" means "a clinical outcome resulting from combination therapy that reflects a greater beneficial effect than the additive effects of the uncombined therapies when administered alone." *Id.* at 7.

Petitioner Pfizer does not dispute the Board's finding for purposes of this proceeding, but notes that the requirement for synergistic results is non-limiting as recited in claims 1 and 4. As explained by the Federal Circuit, where, as here, a method claim requires "express dosage amounts" of a drug, the specifically recited amounts "are material claim limitations" and, thus, "the statement of the intended result of administering those amounts does not change those amounts or otherwise limit the claim." *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001). There, the Court found the claim language "an antineoplastically effective amount" to be a mere "expression of intended result" that "essentially duplicates the dosage amounts recited in the claims." *Id.* That "expression of intended result," the Court held, is "non-limiting." *Id.*

Here, too, the claim term "beneficial synergistic effect" is non-limiting because claim 4, for example, recites the express dosage and frequency of treatment required—namely, 375 mg/m^2 of rituximab with CVP every three weeks for eight

cycles.[4] The only reference to CVP in the specification is a single reference to "standard CVP therapy." Ex. 1001, 13:16. There is no teaching or suggestion in the specification that the amount of CVP must be varied in order to achieve the desired synergistic results; the specification assumes a standard CVP dosage and frequency. Ex. 1002 ¶ 31. Given that the claim requires fixed or standard dosing regimens, the term "beneficial synergistic effect" is non-limiting because it "essentially duplicates the dosage amounts recited in the claims" and is nothing more than an "expression of intended result." *Bristol-Myers Squibb*, 246 F.3d at 1375.

B. "the chimeric anti-CD20 antibody is produced from [particular nucleic acid]"

Claims 3 and 6 include the limitation "wherein the chimeric anti-CD20 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." This

[4] Although the term "beneficial synergistic effect" is arguably non-limiting in claim 1 as well, Petitioner is not making an anticipation argument with respect to that claim. And as explained in further detail below in Section IX, claim 1 would have been obvious to a POSA even if this claim term were limiting.

limitation is simply a description of the antibody "rituximab," and should be construed by the Board to mean (or at least to include) "rituximab."

U.S. Patent No. 5,736,137 ("the '137 Patent"), which issued on April 7, 1998, and would have been known to and publicly accessible by a POSA,[5] disclosed the nucleic acid from which rituximab is produced. Ex. 1010. This patent is referenced on the cover of the '821 patent and is therefore intrinsic evidence. *Phillips*, 415 F.3d at 1317 ("The prosecution history, which we have designated as part of the 'intrinsic evidence,' consists of the complete record of the proceedings before the PTO and includes the prior art cited during the examination of the patent.").

SEQ ID NO : 1 and SEQ ID NO : 2 as listed in the '821 patent are depicted as follows:

<160> NUMBER OF SEQ ID NOS: 2

<210> SEQ ID NO 1
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 1

```
Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro
 1               5                  10                  15

Gly Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser
            20                  25                  30

Tyr Ile His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro
        35                  40                  45

Trp Ile Tyr Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg
    50                  55                  60

Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser
65                  70                  75

Arg Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp
            80                  85                  90

Thr Ser Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
        95                  100                 105

Lys
```

<210> SEQ ID NO 2
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 2

```
Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly
 1               5                  10                  15

Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
            20                  25                  30

Ser Tyr Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu
        35                  40                  45

Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr
    50                  55                  60

Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser
65                  70                  75

Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp
            80                  85                  90

Ser Ala Val Tyr Tyr Cys Ala Arg Ser Thr Tyr Tyr Gly Gly Asp
        95                  100                 105

Trp Tyr Phe Asn Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser
    110                 115                 120

Ala
```

[5] The '137 patent is prior art under 35 U.S.C. § 102(a), (b), and (e).

The ’137 patent describes how rituximab is produced in a section titled “Chimeric Anti-CD20 Antibody Production (C2B8).” Ex. 1010, 21:19–22:15. This section explains that first a light chain region of DNA is extracted from a mouse, and then the “resulting DNA fragment was cloned directly into the TCAE 8 vector in front of the human kappa light chain constant domain and sequenced.” *Id.* at 21:50-52. The DNA sequence from this “murine variable region light chain is set forth in FIG. 4.” *Id.* at 21:53-54. Then a “heavy chain variable region was similarly isolated” from a mouse, *id.* at 21:60-61, and the “sequence for this mouse heavy chain is set forth in FIG. 5,” *id.* at 22:9-10.

The specification describes Figure 4 as “the nucleic acid and amino acid sequences . . . of murine variable region light chain derived from murine anti-CD20 monoclonal antibody 2B8,” and Figure 5 as “the nucleic acid and amino acid sequences . . . of murine variable region heavy chain derived from murine anti-CD20 monoclonal antibody 2B8.” *Id.* at 5:42-49. In short, Figures 4 and 5 disclose the exact same two sequences as in claims 3 and 6 of the ’821 patent. Figure 4 is depicted as follows:

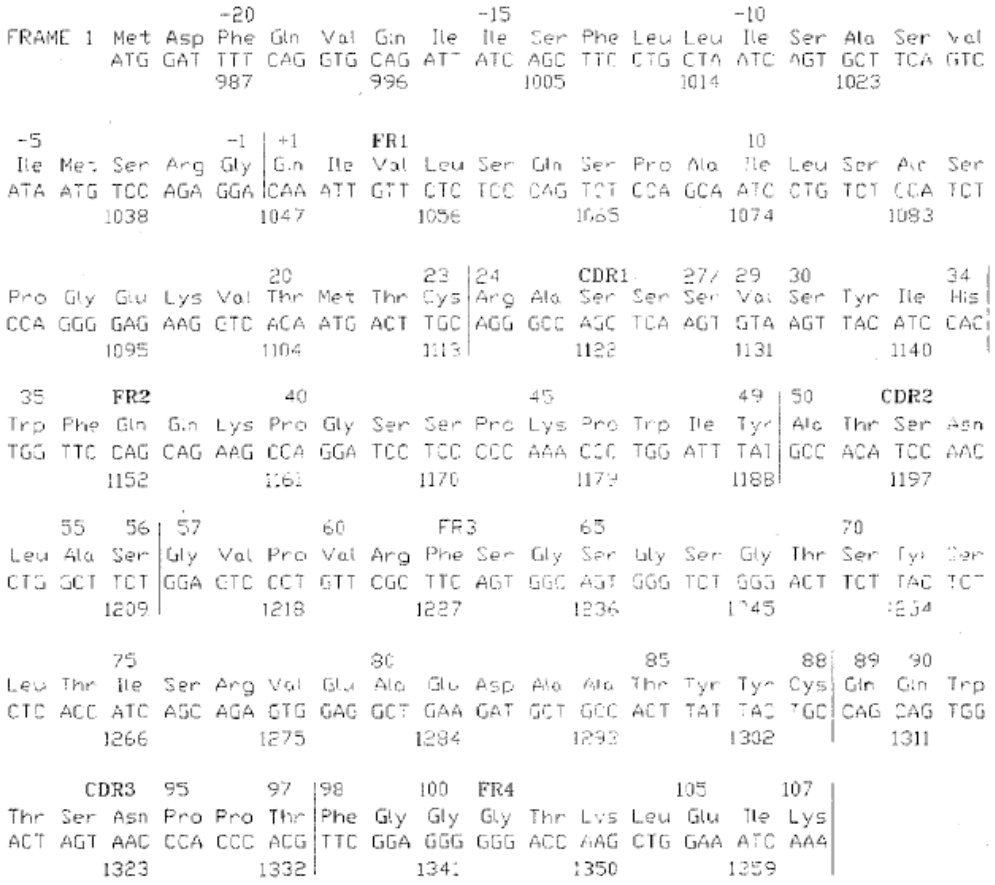

FIG. 4

This light chain sequence discloses the exact same amino acid sequence as SEQ ID NO : 1 in the ’821 patent. And Figure 5 is depicted as follows:

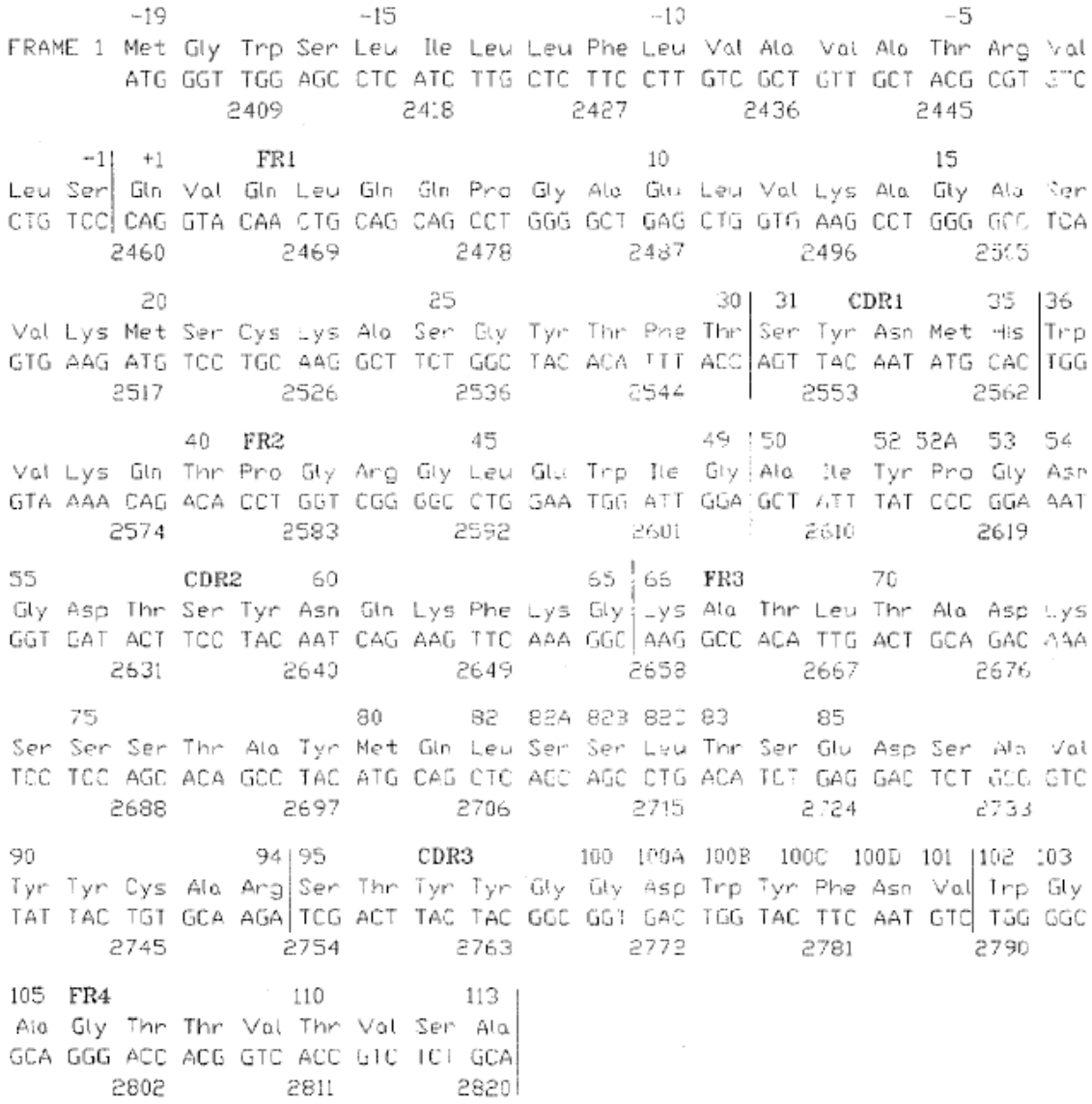
-19 -15 -10 -5
FRAME 1 Met Gly Trp Ser Leu Ile Leu Leu Phe Leu Val Ala Val Ala Thr Arg Val
ATG GGT TGG AGC CTC ATC TTG CTC TTC CTT GTC GCT GTT GCT ACG CGT GTC
2409 2418 2427 2436 2445
-1 +1 FR1 10 15
Leu Ser Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Ala Gly Ala Ser
CTG TCC CAG GTA CAA CTG CAG CAG CCT GGG GCT GAG CTG GTG AAG CCT GGG GCC TCA
2460 2469 2478 2487 2496 2505
20 25 30 31 CDR1 35 36
Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Asn Met His Trp
GTG AAG ATG TCC TGC AAG GCT TCT GGC TAC ACA TTT ACC AGT TAC AAT ATG CAC TGG
2517 2526 2536 2544 2553 2562
40 FR2 45 49 50 52 52A 53 54
Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn
GTA AAA CAG ACA CCT GGT CGG GGC CTG GAA TGG ATT GGA GCT ATT TAT CCC GGA AAT
2574 2583 2592 2601 2610 2619
55 CDR2 60 65 66 FR3 70
Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys
GGT GAT ACT TCC TAC AAT CAG AAG TTC AAA GGC AAG GCC ACA TTG ACT GCA GAC AAA
2631 2640 2649 2658 2667 2676
75 80 82 82A 82B 82C 83 85
Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
TCC TCC AGC ACA GCC TAC ATG CAG CTC AGC AGC CTG ACA TCT GAG GAC TCT GCG GTC
2688 2697 2706 2715 2724 2733
90 94 95 CDR3 100 100A 100B 100C 100D 101 102 103
Tyr Tyr Cys Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly
TAT TAC TGT GCA AGA TCG ACT TAC TAC GGC GGT GAC TGG TAC TTC AAT GTC TGG GGC
2745 2754 2763 2772 2781 2790
105 FR4 110 113
Ala Gly Thr Thr Val Thr Val Ser Ala
GCA GGG ACC ACG GTC ACC GTC TCT GCA
2802 2811 2820

FIG. 5

This figure discloses the exact same heavy chain variable region of 127 amino acids as in SEQ ID NO : 2 in the ’821 patent.[6] Finally, Figures 2A-2F and 3A-3F similarly depict “nucleic acid sequence[s]” of the vector “use[d] in the production of immunologically active chimeric anti-CD20 antibodies,” *id.* at 5:32-41, and these reveal both kappa light chain and human gamma-1 heavy chain regions.

In summary, the limitation of claims 3 and 6 “wherein the chimeric anti-CD20 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” means (or, at a minimum, includes) “rituximab,” because the ’137 patent discloses that rituximab is produced from precisely the nucleic acid described in claims 3 and 6. *See also* Ex. 1002 ¶¶ 32-33.

VIII. STATUS OF PRIOR ART

As shown below and in the Declaration of Petitioner’s expert librarian Dr. Sylvia Hall-Ellis (Ex. 1021), all references that Petitioner relies upon for the ground of unpatentability asserted in this Petition are printed publications that were publicly

[6] SEQ ID NO : 1 and SEQ ID NO : 2 in the ’821 patent are also disclosed as SEQ ID NO : 6 and SEQ ID NO: 9 in the ’137 patent.

accessible before August 11, 1999, or June 15, 2012, and therefore qualify as prior art to the '821 patent under both 35 U.S.C. § 102(b) and § 102(a), with respect to each of the relevant priority dates for which they are being used. *See In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004) ("[P]ublic accessibility has been the criterion by which a prior art reference will be judged for the purposes of § 102(b).").

All of the references described below were published in journals or books that have long been cataloged or indexed in a meaningful way. Ex. 1021 ¶¶ 36-42. Thus, these references were sufficiently accessible to the public, and ordinarily skilled artisans exercising reasonable diligence would have had no difficulty finding copies of them. *Id.*

A. Steward (Ex. 1003)

Steward is an authentic copy of an article from the February 1988 issue of *Cancer*. *Id.* ¶ 36. *Cancer* is currently available in 1,264 libraries and has long been cataloged or indexed in a meaningful way, including by subject. *Id.* Thus, it is—and was—sufficiently accessible to the public interested in the art and an ordinarily skilled researcher or artisan, exercising reasonable diligence, would have had no difficulty finding copies of it. *Id.*

A MARC record from the University of Minnesota Library indicates that the February 1988 issue of *Cancer* containing Steward was catalogued, indexed, and

publicly accessible in at least one library by February 29, 1988. *Id.* Therefore, Steward was available to the public before August 11, 1999 and August 11, 1998 (*id.*) and is a prior-art publication under § 102(b) and § 102(a).

B. **Czuczman (Ex. 1004)**

Czuczman is an authentic copy of an abstract from the November 15, 1995 issue of *Blood*. *Id.* ¶ 37. *Blood* is currently available in 943 libraries, and has long been cataloged or indexed in a meaningful way, including by subject. *Id.* Thus, it is—and was—sufficiently accessible to the public interested in the art and an ordinarily skilled researcher or artisan, exercising reasonable diligence, would have had no difficulty finding copies of it. *Id.*

A MARC record from the University of Minnesota Library indicates that the November 15, 1995 issue of *Blood* containing Czuczman was catalogued, indexed, and publicly accessible in at least one library by November 30, 1995. *Id.* Therefore, Czuczman was available to the public before August 11, 1999 and August 11, 1998 (*id.*) and is a prior-art publication under § 102(b) and § 102(a).

C. **Maloney (Sept.) 1997 (Ex. 1005)**

Maloney (Sept.) 1997 is an authentic copy of an article from the September 1997 issue of *Blood*. *Id.* ¶ 38. A MARC record from the University of Minnesota Library indicates that the 1997 issue of *Blood* containing Maloney (Sept.) 1997 was catalogued, indexed, and publicly accessible in at least one library by September 15,

1997. *Id.* Therefore, Maloney (Sept.) 1997 was available to the public before August 11, 1999 and August 11, 1998 (*id.*) and is a prior-art publication under § 102(b) and § 102(a).

D. **Foon (Ex. 1006)**

Foon is an authentic copy of a book chapter from the 5th edition of *Williams Hematology* edited by Ernest Beutler et al. and is currently available in 364 libraries. *Id.* ¶ 39. A MARC record from the Library of Congress indicates that the 5th edition of this textbook was catalogued, indexed, and publicly accessible in at least one library by August 16, 1994. Therefore, Foon was available to the public before August 11, 1999 and August 11, 1998 (*id.*) and is a prior-art publication under § 102(b) and § 102(a).

E. **Dana (Ex. 1007)**

Dana is an authentic copy of an article from the April 1993 issue of *Journal of Clinical Oncology*. *Id.* ¶ 40. This journal is currently available in 761 libraries and has long been cataloged or indexed in a meaningful way, including by subject. *Id.* Thus, it is—and was—sufficiently accessible to the public interested in the art and an ordinarily skilled researcher or artisan, exercising reasonable diligence, would have had no difficulty finding copies of it. *Id.*

A MARC record from the Library of Congress indicates that the April 1993 issue of *Journal of Clinical Oncology* containing Dana was catalogued, indexed, and

publicly accessible in at least one library by April 30, 1993. *Id.* Therefore, Dana was available to the public before August 11, 1999 and August 11, 1998 (*id.*) and is a prior-art publication under § 102(b) and § 102(a).

F. Marcus (Ex. 1008)

Marcus is an authentic copy of an article from the February 2005 issue of *Blood*. *Id.* ¶ 41. A MARC label from the University of Minnesota Library indicates that the February 2005 issue of *Blood* containing Marcus was catalogued, indexed, and publicly accessible in at least one library by March 15, 2005. *Id.* Therefore, Marcus was available to the public before June 15, 2012 and June 15, 2011 (*id.*) and is a prior-art publication to claims 4-6 under § 102(b) and § 102(a).

G. Pinter-Brown (Ex. 1009)

Pinter-Brown is an authentic copy of a book chapter from the 6th edition of *Manual of Clinical Oncology* edited by Dennis A. Casciato and Mary C. Territo. *Id.* ¶ 42. A MARC record from the Library of Congress indicates that this edition was catalogued, indexed, and publicly accessible in at least one library by June 1, 2008. *Id.* Therefore, Pinter-Brown was available to the public before June 15, 2012 and June 15, 2011 (*id.*) and is a prior-art publication to claims 4-6 under § 102(b) and § 102(a).

IX. ANALYSIS OF GROUNDS FOR TRIAL: AUGUST 1999 PRIORITY DATE

Again, the claims generally recite [1] a method of treating low-grade or follicular NHL with CVP; along with [2] 375 mg/m^2 of the monoclonal antibody rituximab [3] every three weeks for eight cycles (for some claims) [4] with a beneficial synergistic effect (for some claims). For the reasons explained in Part VI.B, a panel of the Board in IPR2017-01095's institution decision held that claims 1-3 are entitled to a priority date no earlier than August 11, 1999. Ex. 1022, 11. The panel further concluded, however, that claims 4-6 are entitled to a priority date no earlier than June 15, 2012. Although Petitioner agrees with the panel's analysis as to claims 4-6 in the related proceeding, out of an abundance of caution, Petitioner shows below that *all* of claims 1-6 would have been obvious over the state of the art as of August 11, 1999, regardless of whether a later priority date applies to claims 4-6. Ex. 1002 ¶¶ 66-90.

By 1999, as confirmed by Steward, Foon, and Dana, the standard therapy for treating low-grade NHL patients was to use chemotherapy, of which CVP in three-week cycles (for between six and ten, more usually six and eight, cycles) was the standard regimen. *See*, *e.g.*, Ex. 1003, Steward at 7; Ex. 1002 ¶ 57. But better therapies were needed. *See* Ex. 1003, Steward at 10-11. A POSA as of August 1999 would have been motivated to add rituximab to improve this CVP regimen because, as taught by Czuczman (published in 1995), rituximab not only has "single agent

efficacy," but also "*synergy* with chemotherapeutic agents and non-overlapping toxicities." Ex. 1004, 11 (emphasis added). Maloney (Sept.) 1997, which also showed that 375 mg/m^2 of rituximab was safe and effective in treating low-grade NHL patients, suggested "combination [of rituximab] with or after *standard chemotherapy*"—which, again, a POSA would read as at least including CVP for this patient population. Ex. 1005, 6-7, 12 (emphasis added); Ex. 1002 ¶¶ 62, 76. As shown below, the claimed invention would have been obvious in view of these references.

A. Ground I: Claims 1-6 would have been obvious over Steward, Czuczman, and Maloney (Sept.) 1997.

1. Claim 1 would have been obvious.

Claim 1 describes "[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." This claim would have been obvious over Steward, Czuczman, and Maloney (Sept.) 1997.

a. A POSA would have been motivated to combine 375 mg/m^2 rituximab and CVP with a reasonable expectation of success in treating patients with low-grade NHL.

In 1988, Steward disclosed that CVP in three-week cycles for six to ten cycles was the standard therapy for low-grade NHL and superior to CHOP because of its lower toxicity: "Treatment comprised initial chemotherapy using three-weekly courses of intravenous vincristine 2 mg on day 1, with oral cyclophosphamide 400 mg/m^2 daily and prednisolone 40 mg daily for 5 days. Treatment was continued to two courses beyond complete remission with a minimum of six and a maximum of ten courses being given." Ex. 1003, 7. The Steward study resulted in a 56% complete response rate, and taught generally that "[e]xperience of the use of combination chemotherapy (predominantly CVP)" has shown complete response rates between 46% to 83%. *Id.* at 10. Steward "demonstrated that combination chemotherapy using CVP induces a complete remission in more than 50% of patients with low-grade NHL, and that the achievement of a CR is associated with a survival advantage." *Id.* at 11.

Although "more aggressive regimens of combination chemotherapy including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)" have been tried, such "studies have not produced obvious improvements of the percentage or duration of responses or survival, and often have resulted in more toxicity." *Id.* at 10; *see also* Ex. 1006, Foon at 42; Ex. 1007, Dana at 11. Thus, Steward taught that

while CVP was the best available therapy for low-grade NHL, "[c]learly different approaches are needed to improve the results of treatment of these patients." Ex. 1003, 10. It is precisely the patients with poor prognostic factors, however, "who would tolerate the toxicity of more aggressive regimens badly." *Id.* at 11.

In 1995, Czuczman reported on a study that combined 375 mg/m^2 of rituximab with CHOP to treat low-grade NHL patients, demonstrating an initial 100% response rate. Ex. 1004, 11. Czuczman explained the rationale for the combination: "single agent efficacy, non cross-resistant mechanism of action, synergy with chemotherapeutic agents and non-overlapping toxicities." *Id.*

Critically, each of these rationales for combining rituximab with CHOP applies equally to CVP. Ex. 1002 ¶ 74. Other prior art references recommended combining rituximab with standard chemotherapy, which includes CVP. For example, Maloney in October 1997 taught that rituximab "increases sensitivity to the cytotoxic effect of chemotherapy/toxins in some resistant human lymphoma cell lines"—i.e., rituximab makes cancerous B-cells more susceptible to the effects of chemotherapy. Ex. 1013, 4; Ex. 1002 ¶ 75. Another reference taught that rituximab makes B-cells more sensitive to chemotherapy and that rituximab-induced apoptosis, i.e., cell death, may be "complemented and completed by the cytotoxic drugs." Ex. 1020, Demidem at 7-8. And in 1998, a prior art reference taught that

"[i]n vitro data suggesting synergy of rituximab with conventional chemotherapy represent the most exciting potential for this agent." Ex. 1033, Grossbard at 1.

Maloney (Sept.) 1997, which also taught the use of 375 mg/m^2 of rituximab for treating low-grade NHL patients, expressly suggested combining this rituximab dose with "standard chemotherapy"—i.e., disclosing that "[a]dditional areas that should be investigated using this new agent include (1) extended and repeated dosing regimens, [and] (2) combination with or after standard chemotherapy"—such as CVP. Ex. 1005, 6-7, 12. And, as Steward taught, CVP was a standard therapy for low-grade NHL patients, and even preferred over CHOP for treating low-grade NHL. Ex. 1003, 10.

Therefore, a POSA looking to treat low-grade NHL would have been motivated to combine the teachings of Czuczman and Maloney (Sept.) 1997 regarding rituximab with the teachings of Steward regarding CVP. That is, a POSA as of August 1999 would have been motivated to combine 375 mg/m^2 of rituximab with the standard CVP chemotherapy to treat patients with low-grade NHL because of rituximab's "single agent efficacy, non cross-resistant mechanism of action, synergy with chemotherapeutic agents and non-overlapping toxicities." Ex. 1004, Czuczman at 11. Steward itself expressed the motivation that better therapies were needed, *see* Ex. 1003, 11 ("[i]mprovements in the survival of patients with advanced-stage low-grade NHL probably will require new approaches to the initial

induction of remission"), and Czuczman taught that rituximab in combination with chemotherapeutic drugs would be such a better therapy. Ex. 1004, 11.

Where a prior-art reference such as Czuczman or Maloney (Sept.) 1997 expressly suggests the combination of two classes of drugs—here, rituximab and standard chemotherapy—that is a "clear motivation to combine" these drugs. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292-93 (Fed. Cir. 2013) (holding that prior art reference teaching a "fixed combination of timolol with an alpha$_2$-agonist" would improve treatment supplied a "clear motivation to combine" the two drugs). Moreover, because CVP and CHOP were two of the most common chemotherapy regimens, Ex. 1002 ¶ 47, they together with rituximab created a "finite number"—i.e., rituximab with CHOP, or rituximab with CVP—of "identified, predictable solutions" to the known problem of treating low-grade NHL. *KSR Int'l. Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007). A set of solutions is "obvious to try" where the prior art provides direction about "which parameters were critical" or "which of many possible choices is likely to be successful," and "finite" where the prior art thereby reduces the options to a set that is "small or easily traversed." *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009) (internal quotation marks omitted). This precedent applies here, where there were only a handful of known, highly effective or widely used options for treating low-

grade NHL patients, and combination therapy was common: CVP, CHOP, and rituximab. Ex. 1002 ¶ 76.

Although it was known that rituximab was synergistic with doxorubicin (missing from CVP), a POSA would have known that rituximab appeared to be synergistic with *multiple* chemotherapeutic drugs. Ex. 1004, Czuczman at 11 (describing "synergy with chemotherapeutic agents"); Ex. 1033, Grossbard at 1 ("In vitro data suggesting synergy of rituximab with conventional chemotherapy represent the most exciting potential for this agent."); Ex. 1002 ¶¶ 74, 76. Czuczman did not say otherwise. And Maloney (Sept.) 1997 suggested combining rituximab with "standard chemotherapy," which was known to at least include CVP. Ex. 1002 ¶¶ 62, 76. The mere existence of more than one obvious alternative does not create nonobviousness; that is, "mere disclosure of more than one alternative does not amount to teaching away from" the invention. *SightSound Techs., LLC v. Apple Inc.*, 809 F.3d 1307, 1320 (Fed. Cir. 2015) (internal quote marks omitted). And, of course, obviousness does not require an "absolute predictability of success." *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

Indeed, a panel of this Board found, in the institution context, that "Czuczman taught that rituximab exhibits 'synergy with chemotherapeutic agents,' without describing any limitation on the type of chemotherapy, such as requiring it to include doxorubicin like CHOP." Ex. 1022, 24. This finding applies equally here.

Additionally, it was obvious to combine rituximab, which destroys cancerous B-cells by attaching to the CD20 antigens expressed on those cells, and CVP, a form of chemotherapy, because of their separate and complementary mechanisms of action. As previously explained, chemotherapy affects cellular metabolism at the level of DNA, cell division, or RNA synthesis, or it interferes with epigenetics. *Supra* p. 10. Rituximab, by contrast, binds to a specific antigen and induces cell death through complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC). Ex. 1002 ¶ 52; *see also* discussion, *supra* Part V.B. Where "[i]t was apparently well-known in the art that two drugs having different mechanisms for attacking [the disease] may be more effective than one," it is at minimum "obvious to try combination therapy." *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1351 (Fed. Cir. 2013); *see also* Ex. 1020, Demidem at 7-8 (rituximab makes B-cells more sensitive to chemotherapy and rituximab-induced apoptosis may be "complemented and completed by the cytotoxic drugs").

In sum, "a skilled artisan would have had reason to combine the teaching[s]" of the Steward, Czuczman, and Maloney (Sept.) 1997 prior-art references to achieve the invention claimed in claim 1, and that "skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine*

Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1069 (Fed. Cir. 2012) (citations omitted).

b. A POSA would have expected the combination to "provide[] a beneficial synergistic effect in the patient."

To the extent the term "beneficial synergistic effect" of claim 1 is even limiting (it is not, as discussed supra at Part VII.A), providing such an effect also would have been obvious to a POSA as of August 1999. In particular, a POSA would have reasonably expected synergy by combining 375 mg/m^2 of rituximab as taught in Czuczman with the CVP regimen of Steward. Ex. 1002 ¶ 77. A panel of this Board agreed, finding in the institution context that "a person of skill in the art would have a reasonable expectation that modifying Czuczman's method to include CVP in place of CHOP would similarly provide a beneficial synergistic effect because Czuczman taught that rituximab exhibits 'synergy with chemotherapeutic agents,' without describing any limitation on the type of chemotherapy, such as requiring it to include doxorubicin like CHOP." Ex. 1022, 24.

That panel was right. As explained above, Czuczman included synergy with chemotherapeutic agents as a rationale for combining rituximab with CHOP, noting the rationales were "single agent efficacy, non cross-resistant mechanism of action, *synergy* with chemotherapeutic agents and non-overlapping toxicities." Ex. 1004, 11 (emphasis added). Czuczman did not teach that synergy was expected solely with

CHOP chemotherapy. Another prior art reference explained that "[i]n vitro data suggesting synergy of rituximab with conventional chemotherapy represent the most exciting potential for this agent," without limiting that conclusion to doxorubicin. Ex. 1033, Grossbard at 1. Thus, a POSA would have been motivated to combine CVP and rituximab and would have reasonably expected synergy with CVP chemotherapeutic agents as well. Ex. 1002 ¶ 77.

Critically, synergy need not have been guaranteed for the invention to have been obvious. "[A] skilled artisan" need only have "a reasonable expectation of success" from combining the teaching of the prior art references to arrive at the claimed invention. *In re Cyclobenzaprine,* 676 F.3d at 1069. And in *Novo Nordisk*, the Federal Circuit held that "[i]t is reasonable that an artisan seeking to combine a known insulin sensitizer (like metformin) with a new insulin secretagogue (like repaglinide) would base his expectations" of synergy upon the performance of other "prior art sensitizer/secretagogue combinations." 719 F.3d at 1355. Thus here, in light of the teaching of Czuczman that rituximab had synergy when combined with various chemotherapy agents and at least with CHOP, "[i]t is reasonable that an artisan seeking to combine [rituximab] with a new [chemotherapy regimen, like CVP] would base his expectations [of synergy] upon prior art [rituximab/chemotherapy] combinations." *Id.*

In sum, given all of the teachings in the prior art discussed above, claim 1 would have been obvious to a POSA as of August 1999.

2. Claim 2 would have been obvious.

Claim 2 describes "[a] method for treating low grade or follicular non-Hodgkin's lymphoma (NHL) comprising administering to a patient 375 mg/m^2 of C2B8 during a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy)." This claim is identical to claim 1 except it does not recite the term "beneficial synergistic effect," and uses the term "C2B8" instead of "rituximab." Patent Owner does not dispute—and this Board has found—that C2B8 is merely another name for rituximab. Ex. 1022, 14-15 ("Patent Owner recognizes that 'C2B8' is a designation for rituximab."); *see also* Ex. 1001, 3:5 (referring to "C2B8" as "Rituximab"). Therefore, claim 2 would have been obvious over the same combination of references and for the same reasons that would have rendered claim 1 obvious. Ex. 1002 ¶ 79.

3. Claim 3 would have been obvious.

Claim 3 is identical to claim 2, except it describes administering a "chimeric anti-CD20 antibody," wherein the antibody is produced by a particular kind of nucleic acid. Patent Owner does not dispute—and this Board has found—that rituximab is a chimeric anti-CD20 antibody. Ex. 1022, 17 ("[I]t is undisputed that

Marcus teaches the use of rituximab, a known and preferred chimeric anti-CD20 antibody.").

As for the recitation of specific nucleic acid sequences from which rituximab is produced, that does not impart patentability to the claims (and thus are non-limiting) because—as this Board held—they merely constitute an "identification and characterization of a prior art material." Ex. 1022, 17 ("[T]hose characterizations include the amino acid sequences and the manner of production. Neither of those characterizations impart patentability to the claim.") (citing *In re Crish*, 393 F.3d 1253, 1258–59 (Fed. Cir. 2004); *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985)). Additionally, as explained in Part VII.B, intrinsic evidence discloses that the recited nucleic acid sequences from which the anti-CD20 antibody is produced in claim 3 merely describes rituximab itself, which is taught in the Czuczman and Maloney (Sept.) 1997 prior-art references. Therefore, claim 3 would have been obvious over the same combination of references and for the same reasons as claims 1 and 2. Ex. 1002 ¶ 81.

4. Claim 4 would have been obvious.

Claim 4 is directed to "[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." This claim is identical to claim 1 except it requires a particular dosing schedule: 375 mg/m^2 of rituximab in combination with CVP *once every three weeks for eight doses*.

As explained above, a POSA would have been motivated to combine rituximab with CVP therapy in light of the Steward, Czuczman, and Maloney (Sept.) 1997 teachings, and would have reasonably expected synergy in light of Czuczman. The additional dosing schedule required by claim 4 cannot save this claim.

A POSA would have found it obvious to administer 375 mg/m^2 every three weeks for eight doses in light of the teachings of Maloney (Sept.) 1997 and Czuczman. The recommended dosing of rituximab according to the U.S. Food and Drug Administration was 375 mg/m^2 for four weeks. Ex. 1011, Rituxan™ Label at 2; Ex. 1012, PDR label at 8. This dosing was disclosed to be safe and effective by Maloney (Sept.) 1997. Ex. 1005, 6-7. Importantly, both the Rituxan™ label and Maloney (Sept.) 1997 made clear that no dose-limiting toxicity was observed, suggesting that administration for more than four weeks could also be appropriate. Ex. 1011, Rituxan™ Label at 2 ("There has been no experience with overdosage in human clinical trials.); Ex. 1012, PDR label at 8 (same); Ex. 1005, Maloney (Sept.) 1997 at 6 ("single doses up to 500 mg/m^2 and 4 weekly doses of 375 mg/m^2 showed

clinical responses with no dose-limiting toxicity"). Thus, for example, the '821 specification described an on-going study of rituximab in weekly doses for 8 weeks. Ex. 1001, 13:10-14.

Czuczman, however, showed that fewer doses of rituximab were also effective. Czuczman administered 375 mg/m^2 rituximab with CHOP but only on weeks 1, 7, 13, 20, and 21. Ex. 1004, 11. This dosing was much less frequent than the recommended weekly dosing, but Czuczman showed the combination of this frequency with CHOP to be highly effective, with an initial overall response rate of 100%. *Id.*; Ex. 1002 ¶ 84. A dosing on this schedule would also have been an obvious treatment option.

Another obvious treatment option would have been to administer rituximab on the exact same cycle as the chemotherapy being administered. Thus, if CVP were the chemotherapy being used, it would have been obvious to administer rituximab once every three weeks, for as long as the treatment continued—for between six and ten weeks, as taught in Steward. *See* Ex. 1003, 7; Ex. 1002 ¶ 85. Administering rituximab on weeks 1, 4, 7, 10, 13, 16—and on weeks 19, 22, 25, and 28 if necessary—would have been known to be effective because the *less* frequent administration in Czuczman was highly effective, and the *more* frequent weekly administration authorized by the FDA-approved label was also known to be effective. Ex. 1005, Maloney (Sept.) 1997 at 6; Ex. 1002 ¶ 85. Therefore, any

choice a POSA would have made within that range (i.e., every three weeks) would have been a matter of routine optimization. *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980) ("[D]iscovery of an optimum value of a result effective variable . . . is ordinarily within the skill of the art."); *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (quoting same).[7]

Moreover, choosing the frequency within that range that aligned with the chemotherapy cycle would have been an obvious treatment option because of the convenience to both doctors and patients of aligning treatments for fewer hospital visitations. Ex. 1002 ¶ 86. This convenience would itself have created a motivation to choose the same dosing cycle for rituximab as for CVP as taught in Steward. *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1262 (Fed. Cir. 2012) ("providing the convenience of an extended release" is a motivation to combine); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1288 (Fed. Cir. 2006) (noting that "[o]nce-a-day dosing provides the usual benefits of convenience"); *see also Cross Med. Prods.,*

[7] The dose of rituximab was known to be a results-effective variable. Ex. 1013, Maloney (Oct.) 1997 at 10 ("A pharmacokinetic analysis of [rituximab] serum levels showed that the C_{max} for both the first and fourth infusions increased with increasing dose. In addition, the C_{max} and serum half-life increased between the first and fourth infusions for most patients.").

Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1322 (Fed. Cir. 2005) ("It has long been the law that the motivation to combine need not be found in prior art references, but equally can be found in the knowledge generally available to one of ordinary skill in the art.") (citations and quote marks omitted); *In re Kahn*, 441 F.3d 977, 987-88 (Fed. Cir. 2006) (similar).

In sum, Steward taught CVP at three-week cycles for six to ten weeks and Maloney (Sept.) 1997 and Czuczman taught that rituximab was effective at 375 mg/m^2 when administered up to once a week (with no dose-limiting toxicity, and thus no necessary limitation on the total number of doses) or as little as every six or seven weeks (as in Czuczman). Any choice in that range would have been obvious as a matter of routine optimization and the choice to align the dosing cycles of rituximab and CVP would also have been obvious for the convenience of minimizing hospital visitations. Thus, the limitation of this claim that rituximab is administered "once every 3 weeks for 8 doses" would have been obvious to a POSA in light of Steward, Czuczman, and the Maloney (Sept.) 1997. Ex. 1002 ¶ 87. At minimum, this dosing frequency would have been obvious to try. *Id.*; *see also KSR*, 550 U.S. at 421 (a solution may be "obvious to try" where "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp"); *Bayer*, 575 F.3d at 1347 (a set of solutions is "obvious to try" where the prior art provides direction about "which parameters were critical" or "which of many

possible choices is likely to be successful," and "finite" where the prior art thereby reduces the options to a set that is "small or easily traversed").

5. Claim 5 would have been obvious.

Claim 5 is identical to claim 4, but does not include the term "beneficial synergistic effect," and describes specifically "C2B8." Patent Owner does not dispute, and this Board found, that C2B8 is another designation for rituximab. *Supra* Part IX.A.2; Ex. 1001 3:5 (referring to "C2B8" as "Rituximab"). Thus, claim 5 would have been obvious over the same combination of references and for the same reasons that would have rendered claim 4 obvious. Ex. 1002 ¶ 88.

6. Claim 6 would have been obvious.

Claim 6 is identical to claim 5, but describes a chimeric anti-CD20 antibody and the nucleic acid sequences from which rituximab is produced. Patent Owner does not dispute—and this Board found—that rituximab is a chimeric anti-CD20 antibody. Ex. 1022, 17 ("[I]t is undisputed that Marcus teaches the use of rituximab, a known and preferred chimeric anti-CD20 antibody."). And as for the nucleic acid sequences from which rituximab is produced, those do not impart patentability for the claims because—as this Board held in IPR2017-01095—they merely constitute an "identification and characterization of a prior art material." *Id.* Additionally, as explained in Part VII.B, intrinsic evidence discloses that the nucleic acid sequences from which the anti-CD20 antibody is produced in claim 6 merely describes

rituximab itself, which is taught in the Czuczman and Maloney (Sept.) 1997 prior-art references. Therefore, claim 6 would have been obvious over the same combination of references and for the same reasons as claims 4 and 5. Ex. 1002 ¶ 90.

B. Ground II: Claims 1-3 would have been obvious over Czuczman, Foon, and Dana.

Claims 1-3 would have been independently obvious over Czuczman, Foon, and Dana. Ex. 1002 ¶¶ 91-92. In fact, a panel of this Board has already instituted claims 1-3 over Czuczman, Foon, and Dana in IPR2017-01095, finding as follows:

> Based on those combined teachings, Petitioner explains persuasively that a person of skill in the art would have been motivated to combine rituximab with CVP instead of CHOP in Czuczman's method with a reasonable expectation of treating low grade NHL because Foon and Dana explain that CVP and CHOP are standard chemotherapy regimens to treat low grade NHL and, among other reasons, CVP is equally effective as CHOP. Further, Petitioner explains persuasively, that a person of skill in the art would have a reasonable expectation that modifying Czuczman's method to include CVP in place of CHOP would similarly provide a beneficial synergistic effect because Czuczman taught that rituximab exhibits "synergy with chemotherapeutic agents," without describing any limitation on the type of chemotherapy, such as requiring it to include doxorubicin like CHOP.

Ex. 1022, 24 (citations omitted).[8] This decision was correct.

Foon and Dana explained that CVP was a preferred treatment for low-grade NHL and that adding doxorubicin did not add to the efficacy but did add significantly to the toxicity. Ex. 1006, Foon at 42 ("intensive combination regimens including doxorubicin also have demonstrated excellent responses for patients with follicular small cleaved cell lymphoma, but there is no evidence that such treatment prolongs survival [over CVP]"); Ex. 1007, Dana at 11 ("the addition of doxorubicin to CVP [i.e., CHOP] results in no improvement in survival"). Thus, a POSA would have been motivated to take the successful rituximab-CHOP regimen of Czuczman and replace CHOP with CVP. Ex. 1002 ¶ 92. For these reasons, claims 1-3 would have been obvious. *Id.*

X. ANALYSIS OF GROUNDS FOR TRIAL: JUNE 2012 PRIORITY DATE

As explained above and in the institution decision for the related Celltrion petition, claims 4-6 are entitled to a priority date no earlier than June 15, 2012. *See supra* Part VI.B. That is because, at a minimum, the parent '202 application did not

[8] Petitioner acknowledges that Celltrion's related petition on this instituted ground could moot this Ground II in this Petition. Petitioner does not seek to duplicate the work of Celltrion in IPR2017-01095, but briefly includes this ground out of an abundance of caution in case that proceeding were terminated.

disclose the use of 375 mg/m^2 of rituximab every three weeks in combination with CVP for eight cycles. *See supra* Part VI.B; Ex. 1002 ¶¶ 38-39. With a priority date of 2012, claims 4-6 would have been anticipated by Marcus. Alternatively, these claims would have been obvious over Marcus, Czuczman, and Pinter-Brown.[9]

A. Ground III: Claims 4-6 are anticipated by Marcus.

1. Claim 4 is anticipated.

Claim 4 describes "[a] method [1] for treating low grade or follicular non-Hodgkin's lymphoma (NHL) [2] comprising administering to a patient a therapeutically effective amount of rituximab during a chemotherapeutic regimen, [3] wherein the chemotherapeutic regimen consists of cyclophosphamide,

[9] A panel of this Board in IPR2017-01095 has instituted proceedings on claims 5 and 6 on the basis of anticipation by Marcus, but not on the basis of claim 4. This Petition includes claim construction arguments not made by Celltrion in IPR2017-01095, which would invalidate claim 4 on this ground as well. Additionally, this Petition presents an obviousness Ground IV for claims 4-6 on the basis of Marcus, Czuczman, and Pinter-Brown, which was not advanced by petitioner Celltrion. In the Celltrion petition, the Board instituted trial on claim 6 on the basis of obviousness over Marcus and the '137 patent (Ex. 1022, 19) but was not presented with an obviousness ground that included Marcus for claims 4 and 5.

vincristine, and prednisone (CVP therapy), [4] wherein the method comprises administering 375 mg/m^2 of rituximab once every 3 weeks for 8 doses, and [5] wherein the method provides a beneficial synergistic effect in the patient."

Marcus taught that 375 mg/m^2 of rituximab once every three weeks for eight doses in combination with CVP "may now be considered as a new standard regimen for the treatment of previously untreated patients with follicular NHL." Ex. 1008, 14. Thus, elements [1]-[4] of claim 4 are disclosed in Marcus. Ex. 1002 ¶ 95. As a panel of the Board held in IPR2017-01095 in the institution context, "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 3 weeks for 8 doses[.]" Ex. 1022, 14.

Additionally, because, as explained above in Section VII.A, the term "beneficial synergistic effect" is non-limiting in claim 4, Marcus discloses each and every limitation of that claim. Claim 4 is therefore anticipated by Marcus. Ex. 1002 ¶ 95.

2. Claim 5 is anticipated.

Claim 5 is similarly anticipated by Marcus. That claim is identical to claim 4, but does not recite the term "beneficial synergistic effect," and describes "C2B8." Specifically, claim 5 is directed to "[a] method for treating low grade or follicular

non-Hodgkin's lymphoma (NHL) comprising administering to a patient 375 mg/m^2 of C2B8 once every 3 weeks for 8 doses during a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy)." As explained above, Patent Owner does not dispute—and this Board has found—that C2B8 is merely another name for rituximab. Ex. 1022, 14-15 ("Patent Owner recognizes that 'C2B8' is a designation for rituximab."); Ex. 1001, 3:5 (referring to "C2B8" as "Rituximab").

Thus, claim 5 is anticipated for the same reasons that render claim 4 anticipated by Marcus. Even if the term "beneficial synergistic effect" were limiting in claim 4, that term is not present in claim 5 and thus claim 5 would be anticipated by Marcus even if claim 4 were not. Ex. 1002 ¶ 96. A panel of this Board instituted trial on claim 5 on this ground. Ex. 1022, 15.

3. Claim 6 is anticipated.

Claim 6 is also anticipated by Marcus. Claim 6 is directed to "[a] method for treating low grade or follicular non-Hodgkin's lymphoma (NHL) comprising administering to a patient 375 mg/m^2 of a chimeric anti-CD20 antibody once every 3 weeks for 8 doses during a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy), wherein the chimeric anti-CD20 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." Patent Owner does not dispute—and this Board has found—that rituximab is a chimeric anti-CD20 antibody. Ex. 1022, 17 ("[I]t is undisputed that Marcus teaches the use of rituximab, a known and preferred chimeric anti-CD20 antibody.").

And as explained above, the nucleic acid sequences from which rituximab is produced do not impart patentability to the claims because—as this Board found in the institution context—they merely constitute an "identification and characterization of a prior art material." *Id.* ("[T]hose characterizations include the amino acid sequences and the manner of production. Neither of those characterizations impart patentability to the claim.") (citing *In re Crish*, 393 F.3d at 1258–59; *In re Thorpe*, 777 F.2d at 697). Additionally, as explained in Part VII.B, intrinsic evidence discloses that the nucleic acid sequences from which the anti-CD20 antibody is produced in claim 6 merely describes rituximab itself, which is taught in Marcus.

Thus, claim 6 is anticipated for the same reasons that would have rendered claim 5 anticipated by Marcus. Ex. 1002 ¶ 96. A panel of this Board in IPR2017-01095 instituted trial on claim 6 on this ground. Ex. 1022, 16-18.

B. Ground IV: Claims 4-6 would have been obvious over Marcus, Czuczman, and Pinter-Brown.

Alternatively, and to the extent that this Board were to find claims 4-6 not anticipated, or that the claim term "beneficial synergistic effect" limits the scope claim 4, claims 4-6 would have been obvious over Marcus, Czuczman, and Pinter-Brown.

1. Claim 4 would have been obvious.

Even if the recited synergy limitation were limiting, claim 4 would nevertheless have been obvious to a POSA over Marcus because it disclosed that such synergy had been demonstrated by combining rituximab with chemotherapy: "Data from in vitro studies suggest that rituximab can sensitize lymphoma cell lines to chemotherapy," and "*a synergistic effect between rituximab and various cytotoxic agents has been demonstrated*." Ex. 1008, 10 (emphasis added). In light of this disclosure, a POSA would have reasonably expected the alleged invention covered by claims 4-6 to be obvious, and that the claimed combination of rituximab and CVP would be synergistic. Ex. 1002 ¶ 97; *In re Cyclobenzaprine*, 676 F.3d at 1069 (a claim is obvious where "a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that [ ] skilled artisan would have had a reasonable expectation of success from doing so."); *In re O'Farrell*, 853 F.2d at 903-04 (obviousness does not require an "absolute predictability of success").

In *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd*., the Federal Circuit held that "[i]t is reasonable that an artisan seeking to combine a known insulin sensitizer (like metformin) with a new insulin secretagogue (like repaglinide) would base his expectations" of synergy upon the performance of *other* "prior art sensitizer/secretagogue combinations." 719 F.3d at 1355. Thus here, in light of the teaching in Marcus that rituximab in combination with various chemotherapies had been shown to be synergistic, "[i]t is reasonable that an artisan seeking to combine a known [anti-CD20 antibody like rituximab] with a new [chemotherapy regimen, like CVP] would base his expectations [of synergy] upon prior art [rituximab/chemotherapy] combinations." *Id.*

Indeed, Patent Owner argued during prosecution that Marcus itself *demonstrated* synergy. Ex. 1026, 9-10 ("These data [in Marcus] point to the beneficial synergistic effect in the patient treated according to the presently claimed invention[.]"). Thus, claim 4 would have been obvious under 35 U.S.C. § 103(a) to a POSA over Marcus, even if not anticipated. Ex. 1002 ¶ 97.

To the extent a POSA would not have reasonably expected synergy in light of Marcus alone, a POSA would have reasonably expected synergy from the method disclosed in Marcus in light of the teachings of other prior art like Czuczman and Pinter-Brown. As discussed above, Czuczman studied rituximab in combination with CHOP in low-grade NHL patients. Czuczman taught that "[t]he rationale for

combination of IDEC-C2B8 [rituximab] with CHOP includes: single agent efficacy, non cross-resistant mechanism of action, *synergy with chemotherapeutic agents* and non-overlapping toxicities." Ex. 1004, 11 (emphasis added). As a panel of this Board recognized in the institution context, "a person of skill in the art would have a reasonable expectation that modifying Czuczman's method to include CVP in place of CHOP would similarly provide a beneficial synergistic effect because Czuczman taught that rituximab exhibits 'synergy with chemotherapeutic agents,' without describing any limitation on the type of chemotherapy, such as requiring it to include doxorubicin like CHOP." Ex. 1022, 24.

Moreover, the Pinter-Brown chapter of the 2009 textbook *Manual of Clinical Oncology* disclosed that rituximab was "the first-line therapy [for low-grade NHL] when combined with CVP." Ex. 1009, 46. On the same page, Pinter-Brown disclosed that "[c]ombinations of rituximab with a variety of chemotherapy regimens are feasible and *are believed to be synergistic*." *Id.* (emphasis added). This textbook confirmed what was already known from Czuczman—that synergy could be reasonably expected from combining rituximab with CVP. *See Novo Nordisk*, 719 F.3d at 1355 ("It is reasonable that an artisan seeking to combine a known insulin sensitizer (like metformin) with a new insulin secretagogue (like repaglinide) would base his expectations [of synergy] upon [other] prior art sensitizer/secretagogue combinations.").

In sum, claim 4 of the '821 patent would have been obvious to a POSA because as explained above, by 2012, the standard therapy for treating low-grade NHL patients was to use R-CVP every three weeks for eight cycles. Ex. 1008, Marcus at 9-14; *see supra* Part X.A.1. A POSA would have further had a reasonable expectation of beneficial synergistic results in light of Marcus's teaching (as well as those in Czucman and Pinter-Brown) that synergy had been demonstrated with a variety of chemotherapy agents. Ex. 1008, Marcus at 10; Ex. 1004, Czuczman at 11; Ex. 1009, Pinter-Brown at 46; Ex. 1002 ¶¶ 97-99.

2. Claims 5 and 6 would have been obvious.

A panel of this Board previously instituted trial on claims 5 and 6 as anticipated by Marcus in IPR2017-01095. Ex. 1022, 14-19. For the same reasons discussed above in Part X.A.2-3, claims 5 and 6 would also have been obvious over Marcus, Czuczman, and Pinter-Brown, at least because Marcus disclosed 375 mg/m^2 of rituximab in combination with CVP every three weeks for eight doses—exactly what is claimed in claims 5 and 6. Ex. 1002 ¶ 99.

C. **Patent Owner's potential rebuttal arguments.**

Patent Owner did not rely on any evidence of secondary considerations to support the application, and Petitioner is aware of none. Even if there were secondary considerations, however, that would not render this patent nonobvious, because even "substantial evidence" of secondary considerations is insufficient to

"overcome the clear and convincing evidence that the subject matter sought to be patented is obvious." *Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d 1476, 1484 (Fed. Cir. 1997).

Furthermore, Petitioner has no burden to identify and rebut secondary considerations. It is the patentee who must first present a prima facie case for such considerations which Petitioners may then rebut. *Sega of Am., Inc. v. Uniloc USA, Inc.*, IPR2014-01453, Paper 11 at 20 (PTAB Mar. 10, 2015). Thus, panels routinely reject arguments against institution based on secondary considerations. *See, e.g.*, *Mylan Pharm. Inc. v. Allergan, Inc.*, IPR2016-01127, Paper 8 at 18 n.4 (PTAB Dec. 8, 2016); *Petroleum Geo-Services, Inc. v. WesternGeco LLC*, IPR2014-01478 Paper 18 at 36 (PTAB Mar. 17, 2015).

Petitioner reserves the right to respond to any new evidence of secondary considerations raised by the patentee.

XI. CONCLUSION

For the foregoing reasons, the Board should institute *inter partes* review and cancel claims 1-6 of the '821 patent as unpatentable.

Dated: December 1, 2017

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

Pursuant to 37 C.F.R. § 42.24, I certify that the foregoing PETITION FOR *INTER PARTES* REVIEW contains 13,853 words (as calculated by the word processing system used to prepare the Petition), excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

Dated: December 1, 2017

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CERTIFICATE OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I certify that, on December 1, 2017, true and correct copies of the foregoing PETITION FOR *INTER PARTES* REVIEW, and all Exhibits thereto, were served by overnight courier service on Patent Owner at the correspondence address of record for U.S. Patent No. 9,296,821 B2, and at another address known as likely to affect service, as follows:

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