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. IPR2018-00231
Patent 9,504,744 B2
Issued: November 29, 2016
Filed: June 20, 2014

Title: TREATMENT OF DIFFUSE LARGE-CELL LYMPHOMA WITH ANTI-CD20 ANTIBODY

PETITION FOR *INTER PARTES* REVIEW

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1010	Arthur T. Skarin & David M. Dorfman, "Non-Hodgkin's Lymphomas: Current Classification and Management," CA Cancer J. Clinicians, 47(6):351-372 (1997) ("Skarin")
1011	W. Hiddemann, "Non-Hodgkin's Lymphoma—Current Status of Therapy and Future Perspectives," Eur. J. Cancer, 31A:2141-2145 (1995) ("Hiddemann I")
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APPENDIX OF CLAIMS

1. A method of treating a >60 year old diffuse large cell lymphoma patient comprising administering anti-CD20 antibody and CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient, wherein the anti-CD20 antibody is administered to the patient in combination with a transplantation regimen.

2. The method of claim 1, wherein the antibody comprises a chimeric anti-CD20 antibody.

3. The method of claim 2, wherein the antibody comprises rituximab.

4. The method of claim 1, wherein the lymphoma is accompanied by bone marrow involvement.

5. The method of claim 1, wherein the transplantation regimen comprises bone marrow transplantation.

6. The method of claim 1, wherein the anti-CD20 antibody and CHOP are administered simultaneously.

7. The method of claim 6, wherein the anti-CD20 antibody and CHOP are administered concurrently.

8. The method of claim 7, wherein the antibody comprises rituximab.

9. The method of claim 6, comprising administering the anti-CD20 antibody on Day 1 of each chemotherapy cycle and the CHOP on Day 1 of each chemotherapy cycle.

10. The method of claim 9, wherein the antibody comprises rituximab.

11. A method of treating a patient with diffuse large cell lymphoma comprising administering rituximab and CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient, wherein the patient is > 60 years old and wherein the rituximab and the CHOP are administered concurrently.

12. A method of treating a >60 year old diffuse large cell lymphoma patient comprising administering rituximab and CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient, wherein the rituximab is administered on Day 1 of each chemotherapy cycle and the CHOP is administered on Day 1 of each chemotherapy cycle.

13. The method of claim 9 comprising administering six or eight chemotherapy cycles, wherein in each chemotherapy cycle a 375 mg/m^2 dose of the anti-CD20 antibody is administered to each patient.

14. The method of claim 13 comprising administering eight chemotherapy cycles, wherein in each chemotherapy cycle a 375 mg/m^2 dose of the anti-CD20 antibody is administered to the patient.

15. The method of claim 12 comprising six or eight chemotherapy cycles, wherein in each chemotherapy cycle a 375 mg/m^2 dose of rituximab is administered to the patient.

16. The method of claim 15 comprising administering eight chemotherapy cycles, wherein in each chemotherapy cycle a 375 mg/m^2 dose of rituximab is administered to the patient.

I. INTRODUCTION

Petitioner Pfizer, Inc. requests *inter partes* review and cancellation of claims 1-16 of U.S. Patent No. 9,504,744 B2 ("the '744 patent"). These claims are directed to methods of treating diffuse large B-cell lymphoma ("DLCL")—an "intermediate" grade of non-Hodgkin's lymphoma ("NHL"), which is a type of cancer—in a specific patient population. Generally speaking, the 16 claims of the '744 patent recite a method of treating [1] DLCL [2] in patients over 60 years old [3] by administering "CHOP" chemotherapy[1] (without any dose limitations), [4] and the monoclonal antibody rituximab at a dose of 375 mg/m^2 [5] for six or eight cycles, and (for some claims) [6] combining this method of treatment with a transplantation regimen. As demonstrated below, the claimed invention would have been obvious to a person of ordinary skill in the art ("POSA") as of the filing date of the provisional application (August 1999), based in part on prior-art printed publications never considered by the Examiner.

[1] CHOP is an acronym used by skilled artisans in the field to describe a chemotherapy regimen that consists of cyclophosphamide, hydroxydaunorubicin (also referred to as doxorubicin or Adriamycin®), Oncovin® (or vincristine), and prednisone (or prednisolone). Ex. 1002 ¶ 1 n.1; Ex. 1001, 8:46-48.

Indeed, Patent Owner added nothing to the teachings of the prior art. Patent Owner did not claim to have invented CHOP chemotherapy to treat DLCL, or to have invented the monoclonal antibody rituximab to treat DLCL. Patent Owner did not claim to have invented the method of using CHOP in combination with rituximab for patients over 60 with DLCL, or the dosing of rituximab, or the frequency of CHOP chemotherapy. Nor did Patent Owner claim to have invented the method of transplantation as salvage therapy if initial therapies failed. Instead, Patent Owner merely claimed to have been the first to combine these prior-art teachings. But combining these teachings was obvious in light of the conventional practices in the art, as evidenced by the prior-art references discussed below.

The standard of care in the art as of August 1999 was to use "full-dose" CHOP chemotherapy in six to eight cycles as a first-line treatment for patients over 60 with DLCL. Ex. 1004, Meyer 1995 at 10. While the prior art taught that the standard six to eight cycles of full-dose CHOP was effective in DLCL patients over 60, toxicity was a concern. Not all elderly patients could complete this therapy because of the toxicity accompanying full-dose CHOP. Ex. 1006, McNeil at 1-2.

A potential, less-toxic alternative to full-dose CHOP was called "mini-CHOP." Two studies (Macedo in 1994 and Martinelli in 1996) taught that six to eight cycles of "mini-CHOP"—that is, CHOP taken in six to eight cycles like the full-dose regimen, but with only half the dose of the highly toxic doxorubicin (the

"H" in "CHOP")—was equally effective as full-dose CHOP in most DLCL patients over 60. Ex. 1003, Macedo at 3; Ex. 1016, Martinelli at 6. But, as Macedo reported, "high risk patients probably need more intensive chemotherapy despite . . . the increased toxicity." Ex. 1003, Macedo at 3.

These references, among others, would have motivated skilled artisans as of August 1999 to seek improved treatments for DLCL patients over 60. In particular, for those patients requiring full-dose CHOP therapy who could not withstand the toxicity, a POSA would have been motived to make the tolerable mini-CHOP regimen more effective. And for those patients who could tolerate full-dose CHOP (which, itself, was not always effective), a POSA would have been motivated to improve efficacy of that therapy without increasing toxicity. The prior art provided a roadmap for addressing both types of patients: adding the monoclonal antibody rituximab to mini-CHOP or to full-dose CHOP.

By 1997, the U.S. Food and Drug Administration ("FDA") approved rituximab for the treatment of low-grade B-cell lymphomas. 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. 1017, Rituxan™ label at 1; Ex. 1018, PDR label at 6. Rituximab was approved at a recommended monotherapy dose of 375 mg/m^2 weekly for four weeks. Ex. 1017, 1; Ex. 1018, 8.

In April 1998, the Link reference taught that, although not yet FDA approved for this use, using rituximab to treat DLCL in combination with full-dose CHOP (i.e., with 50 mg/m^2 of doxorubicin) for the treatment of DLCL was likely superior to, but no more toxic than, using full-dose CHOP alone. Link taught that the combination of full-dose (or "conventional") CHOP and rituximab "represents a tolerable therapy with serious adverse events occurring with a *frequency similar* to that seen with conventional CHOP therapy alone and may offer *higher response rates*." Ex. 1005, 7 (emphases added). In other words, the prior art taught that full-dose CHOP combined with rituximab was at least as good as full-dose CHOP alone, and maybe better—but without any risk of additional toxicity. Ex. 1002 ¶ 64.

In view of ongoing clinical studies of rituximab and full-dose CHOP in patients over 60 with intermediate-grade NHL (which includes DLCL), McNeil specifically suggested combining rituximab with CHOP to improve treatment of patients over 60 who suffer from DLCL. As McNeil explained: "One alternative" to conventional CHOP therapy for patients over 60 "could be CHOP plus the monoclonal antibody [rituximab]." Ex. 1006, 1.

The 1998 Coiffier reference then reported on a study of rituximab specifically in patients over 60 years old with DLCL at eight weekly doses of 375 mg/m^2, or at one 375 mg/m^2 dose followed by seven weekly doses at 500 mg/m^2. The study found no difference between these doses, and taught: "[P]atients [with DLCL] experienced

a significant clinical activity with a low toxicity. Rituximab has significant activity in DLCL and MCL [mantle cell lymphoma] patients and should be tested *in combination with chemotherapy* in such patients." Ex. 1007, 1 (emphasis added). Again, full-dose CHOP was the standard chemotherapy regimen for DLCL patients over 60 years old. *See* Ex. 1006, McNeil at 1-2; Ex. 1004, Meyer 1995 at 10.

As explained in more depth below and in the declaration of Dr. Howard Ozer, in view of the combination of Macedo, Meyer 1995, Link, McNeil, and Coiffier it would have been obvious to a POSA by no later than August 1999 to treat DLCL patients over 60 years old by administering either full-dose CHOP or mini-CHOP chemotherapy with rituximab at a dose of 375 mg/m^2 for six to eight cycles. It would have been equally obvious over only Macedo, Meyer 1995, Link, and McNeil—all prior art references under 35 U.S.C. § 102(b) as well as § 102(a). These references would have rendered claims 11-12 and 15-16 obvious to a POSA.

Finally, it would have been obvious to combine the methods of claims 11-12 and 15-16 with a transplantation regimen, as required by claims 1-10 and 13-14. Well before the critical date, bone marrow transplantation was known to be effective in DLCL patients over 60 if the patients did not sufficiently respond to initial chemotherapy. Ex. 1008, Armitage at 5-6. Transplantation involves the use of high-dose chemotherapy to destroy as many cancerous cells as possible, but this method also destroys healthy cells in the bone marrow. Thus, healthy bone marrow cells are

collected before the high-dose therapy and subsequently reinfused (transplanted) back into the patient after the chemotherapy is completed. *Id.*; Ex. 1002 ¶ 40.

It would have been obvious to combine a rituximab/CHOP chemotherapy regimen with transplantation. For example, the Maloney reference specifically recommended adding rituximab to chemotherapy and transplantation regimens because rituximab does not affect the cells needed for transplantation. Ex. 1009, 10. As Dr. Ozer also explains in his declaration, the Maloney and Armitage references would have motivated a POSA to add a bone-marrow transplantation regimen to rituximab/CHOP therapy if that initial therapy produced an insufficient response—thus rendering obvious claims 1-10 and 13-14, which are directed to the same methods as claims 11-12 and 15-16 but add the limitation "in combination with a transplantation regimen." Ex. 1002 ¶¶ 110-13.

These obvious combination therapies are what the Patent Owner claimed as an invention in the '744 patent. Therefore, all claims of the '744 patent should be cancelled as obvious under 35 U.S.C. § 103(a).

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.* The ’744 patent is not currently subject to any litigation to the best of Petitioner’s knowledge. Petitioner has also filed petitions for *inter partes* review of U.S. Patent Nos. 8,239,172 (IPR2017-01166), 8,557,244 (IPR2017-01167), and 8,821,873 (IPR2017-01168). A panel of this Board has instituted proceedings in IPR2017-01168, but denied institution in IPR2017-01166 and IPR2017-01167. Petitioner has also filed a petition for *inter partes* review of U.S. Patent No. 9,296,821 (IPR2018-00186). The patents challenged in those petitions are also owned by Patent Owner here, and also claim methods of using chemotherapy and rituximab to treat NHL. The previous petitions and the current petition rely on overlapping prior-art references and the same subject-matter expert (Dr. Ozer). Of those other challenged patents, U.S. Patent Nos. 8,557,244 (“the ’244 patent”) and 8,821,873 (“the ’873 patent”) claim priority to the same application to which the ’744 patent claims priority.

Like the ’744 patent, the ’873 patent, over which a panel of this Board has instituted trial, claims methods of using rituximab in combination with CHOP and a transplantation regimen in DLCL patients over 60. The ’244 patent, for which a panel of this Board has denied institution, additionally requires the presence of bulky disease in the DLCL patients over 60—a limitation not present in the ’744 patent.

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 ’744 patent is available for *inter partes* review; and (2) Petitioner is not barred or estopped from requesting review of any claim of the ’744 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 1-16 of the '744 patent pursuant to the following statement of the precise relief requested:

Ground	Claims	Basis	Reference(s)
I	11-12, 15-16	§ 103(a)	Macedo (Ex. 1003); Meyer 1995 (Ex. 1004); Link (Ex. 1005); McNeil (Ex. 1006); Coiffier (Ex. 1007).
II	1-10, 13-14	§ 103(a)	Macedo (Ex. 1003); Meyer 1995 (Ex. 1004); Link (Ex. 1005); McNeil (Ex. 1006); Coiffier (Ex. 1007); Armitage (Ex. 1008); Maloney (Ex. 1009).
III	11-12, 15-16	§ 103(a)	Macedo (Ex. 1003); Meyer 1995 (Ex. 1004); Link (Ex. 1005); McNeil (Ex. 1006).
IV	1-10, 13-14	§ 103(a)	Macedo (Ex. 1003); Meyer 1995 (Ex. 1004); Link (Ex. 1005); McNeil (Ex. 1006); Armitage (Ex. 1008); Maloney (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 Section IX.[2]

IV. LEVEL OF ORDINARY SKILL IN THE ART

The ’744 patent claims priority to U.S. Provisional Application No. 60/148,286, which was filed on August 11, 1999. Without conceding that this priority claim is valid, Petitioner and declarant, Dr. Ozer, use August 11, 1999, as the relevant date for analysis of the level of skill and knowledge of a POSA. Ex. 1002 ¶ 14. All prior-art references relied on by Petitioner to support this petition were published before August 11, 1998, and are thus prior art under both 35 U.S.C. § 102(b) and § 102(a)—with one exception, Coiffier (relied on in grounds I and II), which is prior art under only § 102(a).

In light of the specification, the prosecution history, and the state of the art as of August 11, 1999, a POSA for purposes of the ’744 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.

[2] Petitioner notes that some of the above references may be deemed cumulative, but includes them out of an abundance of caution.

V. THE PRIOR ART AND THE '744 PATENT

A. CHOP chemotherapy and transplantation were "conventional therapies" for patients with intermediate-grade NHL, including patients over 60 with DLCL.

NHL is a cancer that targets the body's lymphatic system. Ex. 1002 ¶ 25. NHL is a type of B-cell lymphoma characterized by the uncontrollable growth of the body's B-cells. *Id.* B-cells are white blood cells that distribute antibodies in the body when they grow into mature cells. They are also referred to as B lymphocytes. *Id.* ¶ 31. 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. 1010, Skarin at 1; Ex. 1002 ¶ 26.

One of the central determining factors for a patient's prognosis was (and remains) her grade of lymphoma: low-, intermediate-, or high-grade NHL. Ex. 1002 ¶ 29. 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. 1011, Hiddemann I at 2-3; Ex. 1010, Skarin at 3-5.

By August 1999, skilled artisans in the field had developed new classification methods for diagnosing patients with NHL. Ex. 1012, Hiddemann II at 1; Ex. 1002

¶ 30. The table below describes the three main classification systems—Kiel, Working Formulation, and REAL—used by skilled artisans in the field at the time of the claimed invention:

Table 1. The three major classifications of NHL

Kiel	Working formulation	R.E.A.L.
Low-grade lymphomas		
Lymphocytic	Small lymphocytic (A)	Lymphocytic
Lymphoplasmocytoid		Lymphoplasmocytoid
		Marginal zone
Centrocytic/centroblastic (follicular, small)	Follicular small cleaved (B)	Follicle centre, follicular
	Follicular mixed (C)	(small and mixed)
Intermediate-grade lymphomas		
Centrocytic/centroblastic (follicular, large)	Follicular large (D)	Follicle centre, large
Centrocytic	Diffuse small cleaved (E)	Mantle cell
Centrocytic/centroblastic (diffuse)	Diffuse mixed (F)	Follicle centre, diffuse (small)
	Diffuse large cell (G)	
High-grade lymphomas		
Immunoblastic	Immunoblastic, large cell (H)	Diffuse large B-cell
Centroblastic	Lymphoblastic, convoluted and non-convoluted (I)	B-precursor large B-cell lymphoma-leukaemia
Lymphoblastic	Lymphoblastic, small-non-cleaved (J)	

Ex. 1011, Hiddemann I at 2, Table 1.

Skilled artisans recognized at this time that treating patients with DLCL would be categorized as an intermediate- or high-grade NHL according to the Kiel classification as well as the REAL classification, *or* as a "working formulation" ("WF," sometimes labeled "IWF") type "G" lymphoma. Ex. 1010, Skarin at 1-3; Ex. 1001, 2:51-67. Lymphomas categorized as intermediate- or high-grade were often studied together, as treatments were considered to be the same. Ex. 1002 ¶ 29; *see also, e.g.,* Ex. 1007 (Coiffier) (administering same therapy to four types of

intermediate- or high-grade lymphoma patients); Ex. 1005 (Link) (administering same therapy to type D, G, and H patients); Ex. 1004 (Meyer 1995) (administering same therapy to five types of intermediate- or high-grade lymphoma patients). As explained by the Hiddemann II 1996 reference, despite the numerous subcategories of lymphomas, "some common features are shared by a variety of different lymphomas that allow them to be grouped into the designated categories." Ex. 1012, 4. Thus, patients with any subtype of intermediate- or high-grade NHL were often treated with the same regimens. Ex. 1002 ¶ 29.

Patients with intermediate- or high-grade NHL, such as DLCL, were treated with chemotherapy and radiation to induce the cancer into remission. Ex. 1014, Foon at 42-43. Chemotherapy interferes with the process of cell division and growth in various way, thus affecting all cells in the body—particularly cancer cells, which divide and grow more rapidly than normal cells. Ex. 1002 ¶ 32. As of 1997, the most favored combination of chemotherapy drugs (because of its effectiveness) for intermediate-grade NHL patients was the drug combination abbreviated CHOP. Ex. 1013, Martelli at 7; Ex. 1002 ¶ 34.

For patients not responding to conventional doses of chemotherapy, a skilled artisan could initiate high-dose chemotherapy and stem cell transplantation from the bone marrow. High-dose chemotherapy destroys as many cancerous cells as possible. However, this process also destroys healthy cells. Stem cells from bone

marrow or peripheral blood are thus collected before the procedure, and transplanted back into the patient after the high-dose therapy. Ex. 1002 ¶¶ 39-40. As the Armitage reference explained, "Autologous BMT [bone marrow transplantation] involves re-establishing hematopoietic cell function in patients after high-dose therapy for cancer." Ex. 1008, 5. This procedure "can be performed in older patients with comparative safety," and bone-marrow transplantation was acceptable for patients up to 70 years old. *Id.* at 5, 6, Table 16-1.

The patentees conceded this state of the prior art in the background section of the '744 patent specification, stating that "[c]onventional therapies [for intermediate- and high-grade lymphomas] have included chemotherapy and radiation, possibly accompanied by either autologous or allogeneic bone marrow or stem cell transplantation." Ex. 1001, 1:42-48. In short, bone-marrow transplantation and chemotherapy (such as CHOP) were "conventional" therapies for treating DLCL.

B. Full-dose CHOP chemotherapy in six to eight cycles was the standard regimen for DLCL patients over 60, but this therapy was too toxic for some patients in this population.

The standard chemotherapy for DLCL patients over 60 was six to eight cycles of CHOP. In 1983, Miller treated three patients over 65 with DLCL with eight cycles of full-dose CHOP. Ex. 1015, 1, 4. All patients receiving eight cycles of CHOP had complete responses. *Id.* at 2, Table 1. Generally, however, the older patients "received fewer courses of initial chemotherapy with CHOP primarily because

prolonged myelosuppression from CHOP did not allow continued treatment at full doses." *Id.* at 4.[3]

In 1995, Meyer confirmed that six to eight cycles of full-dose CHOP every three weeks remained the standard treatment for the elderly, but that less toxic therapies were still needed for certain patients. Meyer 1995 administered full-dose CHOP to several patients over 65 who had intermediate-grade NHL, 47% of whom had DLCL. Ex. 1004, 4, 6, 7 Table 2. All of these patients received six to eight cycles of CHOP, with one of these patients receiving the full eight cycles. *Id.* at 7. Meyer 1995 concluded that "[full-dose] CHOP should remain the standard against which new therapies for elderly patients with intermediate-grade lymphoma are compared," but noted the problem of toxicity, explaining that "elderly patients are susceptible to the toxic effects of full-dose CHOP." *Id* at 4, 10. Thus, Meyer 1995 advised that "studies that assess *strategies specifically directed at reducing the toxicity of CHOP…might be especially important in elderly patients*." *Id.* at 10 (emphasis added).

Around the same time, two other prior art references—Macedo and Martinelli—reported in 1994 and 1996, respectively, on another approach: a "mini-

[3] Myelosuppression occurs when chemotherapy destroys healthy bone marrow cells as well as the cancerous cells. Ex. 1002 ¶ 72 n.3.

CHOP" regimen taken once every three weeks like traditional, full-dose CHOP, but with a reduced dose of the toxic doxorubicin component. Ex. 1003, Macedo at 3; Ex. 1016, Martinelli at 6. Both studies demonstrated that six to eight cycles of this mini-CHOP regimen were much more tolerable in elderly patients but as effective as full-dose CHOP in most patients. For example, Macedo studied 21 patients over 60, all of whom had intermediate-grade NHL and 13 of whom had type G DLCL. Ex. 1003, 3. These patients were given "standard CHOP chemotherapy…with reduced dose of Doxorrubicin [*sic*]"—that is, "mini CHOP"—with only 25 mg/m^2 of doxorubicin compared to the 50 mg/m^2 in full-dose CHOP. *Id.* "The patients received a total of six to eight cycles of mini-CHOP and a consolidation radiation therapy was applied to sites of bulky disease in the limited stages." *Id.* Sixteen patients (76.2%) had a complete response, two patients (9.5%) had a partial response, and only three patients (14.3%) had disease progression. Macedo concluded: "The response rate and toxicity of this chemotherapy compares favorably to other more intensive protocols for elderly patients in the groups of minor risk." *Id.*

Martinelli studied the same mini-CHOP regimen "in patients aged above 60 years,…repeated every 21 days for 6-8 cycles." Ex. 1016, 6. The 37 patients who had "Large B-cell" or "mantle cell" NHL "were treated with acceptable toxicity," and "[t]he overall response rate was 75%." *Id.* Martinelli thus concluded: "This

regimen therefore represents a CHOP variant that retains efficacy and can be safely administered in elderly patients." *Id.*

Unfortunately, higher-risk patients would still need full-dose CHOP. As Macedo explained: "The high risk patients probably need more intensive chemotherapy despite…the increased toxicity." Ex. 1003, 3. Again, however, not all such patients requiring the full-dose CHOP regimen could withstand the toxicity of that regimen. In 1998, McNeil taught that "[o]ne reason for poorer outcomes in older patients is thought to be that [full-dose] CHOP, like some other chemotherapy regimens, is more toxic in this age group" and that "[o]lder patients with good performance status can quite often take three or four treatments, but they have a hard time getting to six or eight [the standard number]." Ex. 1006, 1 (second brackets in original). McNeil explicitly suggested that, as of February 1998, doctors were therefore still "looking for an alternative for patients age 60 and above." *Id.* That is, "the search for other drug combinations that may be as effective but less toxic than CHOP continue[d]." *Id.* at 2.

C. Rituximab was a new therapy for NHL that targeted cancerous B-cells.

The monoclonal antibody rituximab provided skilled artisans with a new avenue for treating elderly DLCL patients. Monoclonal antibodies are proteins or protein chains designed to bind themselves to a specific antigen. They can be "chimeric"—i.e., biologically engineered antibodies that comprise human and

mouse antibody components. Such chimeric antibodies are designed to use the body's natural immune system on the targeted antigen while preventing the body's immune system from recognizing the chimeric antibody as a pathogen and then attacking it. Ex. 1002 ¶ 41. The antibodies can activate the human immune system when they bind to their specific antigens and facilitate the destruction of the cell to which they are bound. Ex. 1001 3:45–4:28; Ex. 1017, Rituxan™ label at 1; Ex. 1018, PDR label at 6.

In late 1997, the FDA approved Rituxan™, the commercial form of rituximab, for the treatment of patients with relapsed or refractory low-grade B-cell NHL. Ex. 1017, 1; Ex. 1018, 6. As a monoclonal antibody, rituximab binds itself to the CD20 antigen found on B-cells, enabling the destruction of these cells. As explained on the Rituxan™ label, rituximab "is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes." Ex. 1017, 1; Ex. 1018, 6. The label explained that its mechanism of action is to "bind[] to the CD20 antigen on B-lymphocytes," which "has been shown to induce apoptosis [cell death] in the DHL-4 human B-cell lymphoma line." Ex. 1017, 1; Ex. 1018, 6. The label explained that the CD20 antigen was "expressed on >90% of B-cell non-Hodgkin's lymphomas." Ex. 1017, 1; Ex. 1018, 6. Rituximab was thus a new treatment alternative because it targeted the CD20 antigen expressed on normal and malignant B-cells in over 90

percent of NHL patients independently of any chemotherapy and radiation. Ex. 1002 ¶¶ 42-44, 48.

D. Link taught that adding rituximab to full-dose CHOP was likely more effective in DLCL patients than full-dose CHOP alone, but without additional toxicity.

As discussed, rituximab initially was approved for treating only low-grade NHL. But by May 1998, more than a year before the date of the claimed invention, a study combining the traditional, full-dose CHOP regimen with rituximab in patients with intermediate- or high-grade lymphoma was published. *See* Ex. 1005, Link at 7. In the Link study, 31 patients (median age 49) were administered "rituximab 375 mg/m2 on day 1 of each 21 day cycle followed 48 [hours] later by CHOP," for six cycles. *Id.* The study included 21 type "G" DLCL patients. *Id.* Of the 31 patients in the study, 30 patients were evaluable for response. *Id.* 63% of the patients had complete responses, 33% of the patients had partial responses, and there was only one progression, meaning that, at a minimum, all but one of the type "G" DLCL patients improved. *Id.*

The study concluded that rituximab in combination with full-dose CHOP did not expose DLCL patients to greater levels of toxicity than they would have been exposed to using full-dose CHOP therapy alone. *See id.*; Ex. 1002 ¶ 63. Link taught that "[t]his regimen [full-dose CHOP and rituximab] represents a tolerable therapy with serious adverse events occurring with a frequency similar to that seen with

conventional [i.e., full-dose] CHOP therapy alone and may offer *higher response rates*." Ex. 1005, 7 (emphases added); Ex. 1002 ¶ 64. Thus, Link taught that adding rituximab to full-dose CHOP in DLCL patients was potentially more effective than full-dose CHOP alone, but not more toxic.

As Dr. Ozer explains, the teaching of Link would have suggested to a POSA that rituximab could be used to treat DLCL patients in combination with any CHOP regimen—either mini-CHOP or, if tolerated, full-dose CHOP—with a reasonable expectation of better efficacy without added toxicity. Ex. 1002 ¶ 64. In fact, Link further taught that "[i]n vitro studies suggest[ed] synergistic cytotoxicity between rituximab and chemotherapy"—i.e., that rituximab and CHOP might be synergistic in their ability to kill cancerous B-cells. Ex. 1005, 7; Ex. 1002 ¶ 64.

E. The prior art suggested combining rituximab and CHOP in patients over 60.

Although Link did not study patients over 60, its teachings led those skilled in the art to recommend combining full-dose CHOP with rituximab to treat elderly DLCL patients. As previously explained, McNeil taught that, because of toxicity concerns, "we should be looking for an alternative [to full-dose CHOP monotherapy] for patients age 60 and above" with intermediate-grade NHL (including DLCL). Ex. 1006, McNeil at 1 (quoting Thomas Habermann, M.D.); *see also id.* at 1-2; Ex. 1013, Martelli at 11-12; Ex. 1002 ¶¶ 56-59. Reporting on ongoing clinical trials with

rituximab, McNeil specifically suggested: "One alternative [for patients over 60] could be [full-dose] CHOP plus the monoclonal antibody [rituximab]." Ex. 1006, 1.

In September 1998, the Coiffier reference confirmed that rituximab was safe and effective in DLCL patients over 60, and recommended combining rituximab with chemotherapy in this patient population. Coiffier studied 54 elderly patients, 30 of whom had DLCL according to the REAL classification system. Ex. 1007, 2; *see also* Part VII.C, *infra*. The median ages of the treatment arms (with different dose levels of rituximab) were 62.5 and 65 years, respectively. *Id.* at 2, Table 1. "The dominant features of this population were a relatively old age, as compared with the published literature, and a high proportion of previously treated patients." *Id.* at 5. The patients were administered rituximab at eight weekly doses of 375 mg/m^2, or at one 375 mg/m^2 dose followed by seven weekly doses of 500 mg/m^2. The study found no difference in efficacy between these doses. *Id.* Of the patients who were diagnosed with DLCL, 37% responded to the rituximab treatment. *Id.* at 3. Coiffier concluded that rituximab should be used in "such patients." *Id.* at 1.

Coiffier taught that rituximab was thus safe and efficacious in DLCL patients over 60 years old. Ex. 1002 ¶ 74. Coiffier further suggested the obvious next step—testing rituximab with chemotherapy. As Coiffier explained: "In this first trial of rituximab in DLCL and MCL [mantle-cell lymphoma], patients experienced a

significant clinical activity with a low toxicity. Rituximab has significant activity in DLCL and MCL patients and *should be tested in combination with chemotherapy in such patients*." Ex. 1007, 1 (emphasis added). Again, at the time, standard chemotherapy for treating DLCL patients over 60 involved full-dose CHOP. *E.g.*, Ex. 1004, Meyer 1995 at 4, 10; Ex. 1002 ¶ 65.

F. The prior art further suggested combining rituximab, chemotherapy, and transplantation.

The prior-art Maloney reference also suggested combining rituximab not just with CHOP, as in Link and McNeil, but also with stem-cell transplantation. Maloney reported in 1997 a study of rituximab in 20 patients with all grades of NHL who had relapsed after previous treatments. Ex. 1009, 3. Maloney taught: "Since this antibody [rituximab] does not appear to impair marrow reserves, it could possibly be used in patients who are myelosuppressed due to recent chemotherapy or following high-dose chemotherapy with ABMT [autologous bone marrow transplantation] or peripheral stem-cell rescue." *Id.* at 10. That is, Maloney taught that rituximab could be used with a transplantation regimen because it does not affect the cells necessary for transplantation. Ex. 1002 ¶ 73. Indeed, Maloney taught that "[r]esponses occurred in patients heavily pretreated with chemotherapy, including aggressive regimens and ABMT." Ex. 1009, 10. This suggested that the combination of rituximab, chemotherapy (e.g., full-dose CHOP or mini-CHOP), and transplantation could lead to clinical responses, i.e. effectiveness. Ex. 1002 ¶ 72.

VI. PATENT CLAIMS, SPECIFICATION, AND FILE HISTORY

A. The ’744 patent claims

The ’744 patent claims are listed above in the appendix of claims. Claims 1 and 11 are representative:

> 1. A method of treating a >60 year old diffuse large cell lymphoma patient comprising administering anti-CD20 antibody and CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient, wherein the anti-CD20 antibody is administered to the patient in combination with a transplantation regimen.
>
> 11. A method of treating a patient with diffuse large cell lymphoma comprising administering rituximab and CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient, wherein the patient is > 60 years old and wherein the rituximab and the CHOP are administered concurrently.

B. The ’744 patent specification

The patent specification explains that “conventional therapies” for patients with intermediate-grade lymphomas “have included chemotherapy and radiation, possibly accompanied by either autologous or allogeneic bone marrow or stem cell transplantation if a suitable don[o]r is available, and if the bone marrow contains too many tumor cells upon harvesting.” Ex. 1001, 1:42-46. As a conventional therapy, “[a]utologous bone marrow transplantation is often a successful accompaniment to

myeloablative therapy in helping to restore the immune system to patients who have undergone radiotherapy or chemotherapy." *Id.* at 6:14-17.

The claimed invention includes "methods comprising the administration of rituximab and CHOP." "Depending on the particular patient, said chemotherapy may be administered simultaneously or sequentially in either order." *Id.* at 3:39-41. "'Simultaneously' means either concurrently or during the same time period such that the circulating half-lives of the therapeutic agents overlaps." *Id.* at 3:41-44.

The specification instructs a POSA that, "[w]hen there is bone marrow involvement," rituximab can be administered at all stages—it "can be administered at induction, in vivo purging, mobilization, conditioning, post-transplant reinfusion and at any other time during bone marrow or stem cell transplant for the purpose of improving the survival rate of transplant recipients." *Id.* at 6:23, 6:28-33. "'Induction' is meant to refer to the initial therapies aimed at achieving induction of remission. Typically, induction involves the administration of some type of chemotherapy, i.e., CHOP." *Id.* at 6:33-37.

C. Prosecution history

The application for the '744 patent, No. 14/310,167 filed on June 20, 2014, was a continuation of the application that became the '873 patent, which was a divisional of the application that became the '244 patent. Original independent claim 1 of the '167 application was directed to a method of treating a patient with

DLCL comprising administering an anti-CD20 antibody and chemotherapy. Ex. 1024, 22. The eight dependent claims specified rituximab, CHOP, and patients > 60 years old, with original claim 6 specifying the method of claim 1 "in combination with a transplantation regimen." *Id.*

The Examiner initially rejected claims 1-4, 6, and 7 as anticipated by Link and/or Tsai, another prior art reference. Ex. 1025, 3-4. The Examiner further rejected claims 1-4 and claim 9 as obvious over Link and Coiffier. *Id.* at 6. As the Examiner concluded: "One would have been motivated to use the method of Link to treat patients greater than 60 years old, because Coiffier shows that rituximab is useful in the treatment of patients greater than 60 years old." *Id.* Further: "One would have had a reasonable expectation of success because Coiffier teaches that the toxicity is low for rituximab and because Link teaches that the toxicity of rituximab does not overlap with the toxicity of CHOP therapy." *Id.* at 6-7. All the claims were further rejected on double-patenting grounds in light of the '873 patent. *Id.* at 9.

The Applicants amended claim 1 to incorporate original claim 9—specifying patients > 60 years old, a limitation that had not been rejected on anticipation grounds. Ex. 1026, 4. The Applicants then sought to overcome the Link and Coiffier rejection by arguing that "[t]he art prior to August 1999 taught away from combining rituximab and CHOP to treat elderly patients (>60 years old)" because, "[a]t that

time, even CHOP alone was thought to perhaps be too toxic for certain elderly patients." *Id.* at 5. They argued a POSA would not have known whether a combination of rituximab and full-dose CHOP "might be too toxic in such patients." *Id.* They filed a terminal disclaimer to overcome the double patenting objections. *Id.* The Applicants also added claims reciting the simultaneous or concurrent administrations of rituximab and CHOP. *Id.* at 3.

In a final rejection, the Examiner maintained an obviousness objection over Link and Coiffier, in further view of Meyer 1998, a reference that taught that "standard CHOP therapy in elderly patients with aggressive [NHL] (including patients with [DLCL]) can be safely administered to elderly patients." Ex. 1027, 8. The Examiner thus implicitly rejected applicant's teaching-away argument. The Examiner further rejected as obvious the limitations reciting concurrent and simultaneous administration of rituximab and CHOP in light of the specification's definition of "simultaneous" to include overlapping half-lives, which covered the treatment regimen of Link (which administered rituximab and full-dose CHOP 48 hours apart). *Id.* at 6-7.

The Applicants requested further examination after amending the claims once more to incorporate original claim 6—"in combination with a transplantation regimen"—into claim 1. Ex. 1028, 5. The Applicants then argued they traversed the rejection over Meyer 1998 because "[e]ven using the standard dose" of CHOP

and an additional agent intended to reduce toxicity, "20% of patients in the standard-dose group had to stop therapy prematurely." *Id.* at 7. The Applicants also argued that the prior art "taught away" because "even CHOP alone was thought to perhaps be too toxic for certain elderly patients." *Id.* Because other attempts at reducing the toxicity of full-dose CHOP had failed, Applicants argued, a POSA would not have known whether the combination treatment "might be too toxic" or "would reduce the efficacy." *Id.* at 8.

The Examiner allowed the claims, stating only that the rejection was withdrawn "in view of the amendment to claim 1 incorporating the limitations of claim 6 (now cancelled), which was not rejected over the cited prior art." Ex. 1029, 7. That is, the only stated reason for allowing the claims was that the Applicants incorporated "in combination with a transplantation regimen" into claim 1.

VII. CLAIM CONSTRUCTION

The terms of the '744 patent should be given their broadest reasonable interpretation, which in this case is their plain and ordinary meaning. MPEP § 2111.01.

A. "in combination with a transplantation regimen"

As explained in more detail by Dr. Ozer, claim 1 requires that the anti-CD20 antibody (e.g., rituximab) be administered "in combination with" a transplantation regimen. This includes, but is not limited to, the administration of the anti-CD20

antibody (e.g., rituximab) at the "induction" of CHOP chemotherapy but before the actual collecting or transplanting of stem cells. Ex. 1002 ¶¶ 78-82; *see also Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("only those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy"). As the specification states, "rituximab can be administered at induction, in vivo purging, mobilization, conditioning, post-transplant reinfusion and at any other time during bone marrow or stem cell transplant for the purpose of improving the survival rate of transplant recipients." Ex. 1001, 6:28-33. The specification next defines "induction" as "refer[ring] to the initial therapies aimed at achieving induction of remission," typically involving "the administration of some type of chemotherapy, i.e., CHOP." Ex. 1001, 6:33-37; *see also id.* at 6:20-72. Thus, "in combination with a transplantation regimen" includes the use of transplantation after "induction" therapy with rituximab and chemotherapy. Ex. 1002 ¶ 82.

B. "CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy"

This claim term does not contain any dosing requirements or otherwise limits the amount of each drug. Thus, as explained by Dr. Ozer, a POSA would understand this term to include at least a "full-dose" CHOP regimen and the "mini-CHOP" regimen that used only half the dose of doxorubicin. Ex. 1002 ¶ 83. Indeed, Dr.

Ozer explains that he used both full-dose CHOP and mini-CHOP to treat DLCL patients over 60 before August 1999. *Id.*

C. "diffuse large cell lymphoma"

In IPR2017-01167, a panel of this Board construed this claim term "for purposes of [the institution] Decision" as the "Grade G designation" in the IWF or "Working formulation" classification system. Ex. 1021, 5. For purposes of the present petition, however, a POSA would understand the claim term "diffuse large cell lymphoma" to include not only Type G in the IWF classification system, but also "DLCL" under the REAL classification system. Ex. 1002 ¶¶ 84-86.

In the specification, Patent Owner explained that "for the purposes of the methods described herein, intermediate- and high-grade lymphomas are defined as those designated in the 'Working Formulation' established in 1982." Ex. 1001, 2:54-57. However, the specification also discusses the "REAL classification system" and notes that the "intermediate" or "high-grade" lymphomas per that classification system "would . . . benefit from the therapeutic methods of the present invention." *Id.* 3:1-20. Additionally, the specification cites to the Coiffier reference in support of the invention, and explains that, in Coiffier, "[p]atients with diffuse large-cell lymphoma (N=30) had an [overall response rate] of 37%." *Id.* 7:30-45.

The Coiffier reference reported on a study of 30 DLCL patients according to the REAL classification. Ex. 1007, 3; *see also* Ex. 1002 ¶¶ 84-86.[4]

D. "concurrently"

The specification does not define the claim term "concurrently." It does, however, define the term "simultaneously" as including concurrently: "'Simultaneously' means either concurrently or during the same time period such that the circulating half-lives of the therapeutic agents overlaps." Ex. 1001, 3:41-44. In view of this definition and the intrinsic record as a whole, and as Dr. Ozer explains, a POSA would understand the term "concurrently" as requiring the infused drugs in the claimed combination therapy to be administered on the same day during the same hospital visit, whereas "simultaneously" would also include infusing these drugs on different days as long the circulating half-lives of the therapeutic agents overlap. Ex. 1002 ¶ 88; *accord* Ex. 1027, 7 (Examiner's similar construction of the term "concurrently").

[4] In IPR2017-01167, the Board found only that the term "DLCL" included only "Type G," and excluded "Type F" and "Type H," under the IWF system. There was no finding, nor did any of the parties even argue, whether the claim term included "DLCL" under other classification systems, such as REAL, which it plainly does.

VIII. PRIOR ART STATUS

As shown below and in the Declaration of Petitioner's expert librarian Dr. Scott Bennett (Ex. 1023), all but one of the references that Petitioner relies upon for the ground of unpatentability asserted in this Petition are printed publications that were publicly accessible before August 11, 1998, and therefore qualify as prior art to the '744 patent under 35 U.S.C. § 102(b) and § 102(a). *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)."). Coiffier is a printed publication that was publicly accessible as of September 1998, i.e. before August 11, 1999, and therefore qualifies as prior art to the '744 patent under 35 U.S.C. § 102(a).

All of the references described below were published in journals or books that have long been cataloged or indexed in a meaningful way. Ex. 1023 ¶¶ 37-109. 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.* Moreover, each date stamp on each of the references has the general appearance of date stamps that libraries have long affixed to periodicals, and there is no reason to believe it was affixed by anyone other than library personnel, or on any other date than the date stamped on the reference. *Id.*

A. Armitage (Ex. 1008)

Armitage is an authentic copy of a book chapter from the 1995 textbook *Clinical Oncology* edited by Martin D. Abeloff et al., and is held in 176 libraries worldwide. *Id.* ¶ 83. A date stamp from the Statewide Illinois Library catalog indicates that the book containing Armitage was processed on July 3, 1996. *Id.* ¶ 85. Therefore, Armitage was available to the public before August 11, 1998, and is a prior-art publication to the claims under § 102(b) and § 102(a).

B. Meyer 1995 (Ex. 1004)

Meyer 1995 is an authentic copy of an article from the September 1995 issue of *Journal of Clinical Oncology*, a publication first published in 1983 and held by 774 libraries worldwide. *Id.* ¶¶ 88-93. The *Journal of Clinical Oncology* 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 date stamp from the University of Wisconsin Library indicates that the issue of the *Journal of Clinical Oncology* containing Meyer 1995 was date stamped, received, and processed by that library on September 12, 1995. *Id.* ¶ 94. Therefore, Meyer 1995 was available to the public before August 11, 1998 and is a prior-art publication under § 102(b) and § 102(a).

C. Macedo (Ex. 1003)

Macedo is an authentic copy of an abstract from the November 15, 1994 issue of *Blood*. *Blood* has long been cataloged or indexed in a meaningful way, including by subject. *Id.* ¶ 98-102. 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.* Public records confirm that *Blood* is a periodical that was first published in 1946 and is held by 953 libraries worldwide. *Id.* ¶ 105. A date stamp from the National Library of Medicine indicates that the November 15, 1994, issue of *Blood* containing Macedo was processed by that library on November 25, 1994. *Id.* ¶ 106. Accordingly, Macedo was available to the public before August 11, 1998, and is a prior-art printed publication to the '744 patent under 35 U.S.C. § 102(b) and § 102(a).

D. Maloney (Ex. 1009)

Maloney is an authentic copy of an article from the October 1997 issue of *Journal of Clinical Oncology*. As explained, this journal was sufficiently accessible to the public interested in the art. *Id.* ¶¶ 58-63. A date stamp from the University of Wisconsin Library indicates that the issue of the *Journal of Clinical Oncology* containing Maloney was date stamped, received, and processed by that library on October 14, 1997. *Id.* ¶ 64. Therefore, Maloney was available to the public before August 1998 (*id.* ¶ 65) and is a prior-art publication under § 102(b) and § 102(a).

E. McNeil (Ex. 1006)

McNeil is an authentic copy of a news report by Caroline McNeil published in the February 18, 1998, issue of the *Journal of the National Cancer Institute*. *Id.* ¶¶ 49-53. Public records confirm that the *Journal* is a periodical that was first published in 1940 and is held by 1,302 libraries worldwide. *Id.* ¶ 54. A date stamp from the University of Illinois at Urbana-Champaign Library indicates that the February 18, 1998, issue of the *Journal of the National Cancer Institute* containing McNeil was processed by that library on March 13, 1998. *Id.* ¶ 55. Accordingly, McNeil was available to the public before August 11, 1998 (*id.* ¶ 56) and is a prior-art publication under § 102(b) and § 102(a).

F. Link (Ex. 1005)

Link is an authentic copy of an excerpt from the *Program Proceedings of the Thirty-Fourth Annual Meeting of the American Society of Clinical Oncology*, May 16–19, 1998, Los Angeles, California, Volume 17 (1998). *Id.* ¶¶ 37-42. Public records indicate that the program proceedings of ASCO's meetings, including the Link excerpt, are held by 344 libraries worldwide. *Id.* ¶ 45. In particular, Link includes a date stamp printed with the words: "The Library – U.C. Berkeley," "04-28-98." *Id.* ¶ 46; *see* Ex. 1005, 1. Therefore, Link was available to the public before August 11, 1998 and is as a publicly accessible printed publication under 35 U.S.C. § 102(b) and § 102(a).

G. Coiffier (Ex. 1007)

Coiffier is an authentic copy of a news report by B. Coiffier published in the September 15, 1998 issue of *Blood*. Ex. 1023 ¶¶ 68-73. A date stamp from the University of Wisconsin Library indicates that the September 15, 1998, issue of *Blood* was processed by that library on September 15, 1998. *Id.* ¶ 75. Accordingly, Coiffier was available to the public before August 11, 1999, and is a prior-art printed publication to the '744 patent under 35 U.S.C. § 102(a).

IX. ANALYSIS OF GROUNDS FOR TRIAL

The '744 patent would have been obvious to a POSA. The 16 claims are directed toward using 375 mg/m^2 of rituximab in combination with CHOP (with no dose limitation, i.e., full-dose CHOP or mini-CHOP) for six or eight cycles in DLCL patients over 60, in further combination (for some of the claims) with a transplantation regimen. All the claims would have been obvious.

Link taught that the efficacy of conventional chemotherapy—e.g., six cycles of full-dose CHOP therapy—for treating DLCL patients over 60 could be improved, without increasing toxicity, by adding 375 mg/m^2 of rituximab. *See* Ex. 1005, 7; *see also* Ex. 1004, Meyer 1995 at 10 (six-to-eight cycles of full-dose CHOP remains standard therapy for patients over 60). McNeil specifically suggested that "[o]ne alternative" to conventional full-dose CHOP for elderly DLCL patients "could be CHOP plus the monoclonal antibody [rituximab]." Ex. 1006, 1. In view of Link

and McNeil, it would have been obvious to a POSA to improve the efficacy of not only a full-dose CHOP regimen, but also the mini-CHOP regimen disclosed by Macedo, by co-administering rituximab. Ex. 1002 ¶¶ 95-99. This is particularly true in view of Coiffier, which confirmed that "Rituximab has significant activity in DLCL and MCL patients [including those over 60] and *should be tested in combination with chemotherapy in such patients*." Ex. 1007, 1 (emphasis added).

As shown below, all claims would have been obvious because the prior art also would have motivated a POSA to add a transplantation regimen if initial induction therapy with rituximab and CHOP failed to produce sufficient results. Ex. 1008, Armitage at 5-6; Ex. 1009, Maloney at 10; Ex. 1002 ¶¶ 110-13. And a skilled artisan would have reasonably expected success in view of the encouraging teachings of the prior art. *See In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988); Ex. 1002 ¶ 113.

A. Ground I: Claims 11-12 and 15-16 would have been obvious over Macedo, Meyer 1995, Link, Coiffier and McNeil.

Claims 11-12 and 15-16 are generally directed to treating DLCL patients over 60 years old by combining 375 mg/m^2 of rituximab with CHOP chemotherapy in six or eight cycles. These claims all would have been obvious to a POSA as of August 1999 over Macedo, Meyer 1995, Link, Coiffier, and McNeil. Ex. 1002 ¶¶ 91-106.

1. Claim 11 would have been obvious.

Claim 11 is an independent claim directed to "[a] method of treating a patient with diffuse large cell lymphoma comprising administering rituximab and CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient, wherein the patient is > 60 years old and wherein the rituximab and the CHOP are administered concurrently." Claim 11 would have been obvious to a POSA as of August 1999. Ex. 1002 ¶ 92.

a. The prior art disclosed using full-dose CHOP or mini-CHOP to treat DLCL patients over 60.

The prior art taught that full-dose CHOP was the standard for treating DLCL patients over 60. Meyer 1995 confirmed that six to eight cycles of full-dose CHOP every three weeks remained the standard treatment for elderly DLCL patients. Meyer administered full-dose CHOP to several patients over 65 who had intermediate-grade NHL, 47% of whom had DLCL. Ex. 1004, 4, 6, 7 Table 2. All of these patients received six to eight cycles of CHOP, with one of these patients receiving the full eight cycles. *Id.* at 7. Only two patients did not complete six cycles, meaning at least seven DLCL patients over 65 received at least six cycles of full-dose CHOP. *Id.* Meyer concluded that "[full-dose] CHOP should remain the standard against which new therapies for elderly patients with intermediate-grade lymphoma are compared." *Id.* at 4, 10.

In 1996, Macedo, which was not before the Examiner, further disclosed that a "mini-CHOP" regimen (where the amount of doxorubicin, which causes toxic side effects, was reduced by half) of six to eight cycles could yield efficacy comparable to traditional, full-dose CHOP therapy in most DLCL patients over 60. In particular, this mini-CHOP regimen was effective to produce a complete response in 16 out of 21 (76.2%) patients. Ex. 1003, 3. Macedo thus confirmed that the claim limitations requiring a method of treating a DLCL patient over 60 years old with CHOP chemotherapy (covering both full-dose CHOP and mini-CHOP) would have been known to a POSA as of August 1999. Ex. 1002 ¶ 93.[5]

[5] *See also* Ex. 1001, 1:42-46 (patent specification explaining under "background of the invention" that "[c]onventional therapies [for intermediate- and high-grade lymphomas] have included chemotherapy"); *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1570 (Fed. Cir. 1988) ("A statement in a patent that something is in the prior art is binding on the applicant and patentee for determinations of anticipation and obviousness."); *Ex Parte Xintian E. Lin & Qinghua Li*, 2016 WL 6560248, at *1 (PTAB, Nov. 2, 2016) (describing "background section of the specification" as "Applicant Admitted Prior Art").

b. The prior art would have motivated a POSA to combine rituximab and full-dose CHOP or mini-CHOP with a reasonable expectation of success.

The prior art would have also motivated a POSA as of August 1999 to combine full-dose CHOP or mini-CHOP with rituximab.

As explained, Meyer 1995 taught that full-dose CHOP in at least six cycles was standard therapy for DLCL patients over 60. However, not all patients could withstand the toxicity of full-dose CHOP. McNeil explained: "One reason for poorer outcomes in older patients is thought to be that CHOP, like some other chemotherapy regimens, is more toxic in this age group," and "[o]lder patients with good performance status can quite often take three or four treatments, but they have a hard time getting to six or eight [the standard number]." Ex. 1006, 1 (brackets in original). McNeil explicitly suggested that, as of February 1998, doctors were therefore still "looking for an alternative for patients age 60 and above" and that "the search for other drug combinations that may be as effective but less toxic than [full-dose] CHOP continues." *Id.* at 1-2.

One alternative was the mini-CHOP regimen disclosed by Macedo. However, even Macedo noted that "high-risk" patients still would need the full-dose CHOP therapy, and that this would result in increased toxicity in these particular patients. Ex. 1003, 3 ("The response rate and toxicity of this chemotherapy compares favorably to other more intensive protocols for elderly patients in the groups of

minor risk. The high risk patients[, however,] probably need more intensive chemotherapy despite…the increased toxicity.").

Thus, a POSA would have been motivated to find improved treatments for DLCL patients over 60—particularly for those who needed the efficacy of a full-dose CHOP regimen but could not withstand the toxicity. In view of the prior art, it would have been obvious to a POSA that adding rituximab either to the mini-CHOP treatment taught by Macedo, or to conventional full-dose CHOP discussed in Meyer 1995. McNeil specifically suggested that one "alternative" to CHOP monotherapy in patients over 60 "could be CHOP plus the monoclonal antibody [rituximab]." Ex. 1006, 1.

The Link and Coiffier references confirmed this suggestion. Although not specifically tested in elderly patients, Link taught that full-dose CHOP in combination with rituximab is at least as effective as, but no more toxic than, full-dose CHOP alone. Ex. 1002 ¶ 95. Link studied the combined use of CHOP and rituximab in six cycles in 21 patients with DLCL. Ex. 1005, 7. All but one patient improved, with 63% having a complete response, thus teaching that CHOP in combination with rituximab successfully treats DLCL. *Id.* Link further taught that adding rituximab to a regimen of full-dose CHOP is likely more effective than full-dose CHOP alone, but *does not add to the toxicity*. *Id.* ("This regimen represents a tolerable therapy with *serious adverse events occurring with a frequency similar to*

that seen with conventional CHOP therapy alone and may offer higher response rates.") (emphases added). Link further taught that "[i]n vitro studies suggest[ed] synergistic cytotoxicity between rituximab and chemotherapy." *Id.*

Coiffier then confirmed that 375 mg/m^2 of rituximab was safe and effective in patients over 60 with DLCL, and even recommend studying it in combination with standard chemotherapy regimens in such patients: "In this first trial of rituximab in DLCL and MCL [mantle-cell lymphoma], patients [including patients over 60] experienced a significant clinical activity with a low toxicity. Rituximab has significant activity in DLCL and MCL patients and *should be tested in combination with chemotherapy in such patients*." Ex. 1007, 1 (emphasis added).

In view of the combined teachings of these references, it would have been obvious to a POSA as of August 11, 1999, to add rituximab to a CHOP chemotherapy regimen when treating DLCL patients over 60. In particular, it would have been obvious to add rituximab to a full-dose CHOP regimen for those patients who could successfully withstand six-to-eight cycles. Ex. 1002 ¶ 95. Such a treatment would likely have been even more effective than full-dose CHOP, but without any additional toxicity. Ex. 1005, Link at 7.

Additionally, it would have been obvious to add rituximab to the mini-CHOP regimen of Macedo to achieve more efficacy than mini-CHOP alone, but without the elevated toxicity of a full-dose CHOP regimen, for those patients who could not

withstand the toxicity of full-dose CHOP. Ex. 1002 ¶ 96. A POSA would have expected that rituximab would similarly add to the efficacy of mini-CHOP without adding to the toxicity, as it did with full-dose CHOP. *Id.*

In fact, the express teachings of McNeil and Coiffier provided a "clear motivation to combine" CHOP (including both full-dose and mini-CHOP) and rituximab for treating DLCL patients over 60. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292-93 (Fed. Cir. 2013) (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). Additionally, given Link's teaching that the anti-CD20 antibody rituximab could likely be combined with full-dose CHOP for additional efficacy but without additional toxicity—and because rituximab was the only available anti-CD20 antibody—these prior-art references would also have given a POSA a "finite number of identified, predictable solutions" to the known problem of treating DLCL patients over 60 years old more effectively without increasing toxicity—with a reasonable expectation of success. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007); *see also* Ex. 1002 ¶ 96.

Moreover, it was obvious to combine rituximab and full-dose or mini-CHOP therapies to treat DLCL patients over 60 because these therapies have separate and complementary mechanisms of action. Rituximab destroys cancerous B-cells by attaching to the CD20 antigens expressed on those cells, lysing the membranes, and

thus inducing cell death. Ex. 1002 ¶¶ 42-44. In contrast—and as explained above—chemotherapy (such as the CHOP regimen) attacks the cell division process through numerous other mechanisms. Ex. 1002 ¶ 32; *see also* Ex. 1033, 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"). 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 Accord Healthcare Inc., USA v. Daiichi Sankyo Co.*, IPR2015-00864, Paper 104 at 19–20 (PTAB Sept. 12, 2016) (quoting *Novo Nordisk*).

In sum, "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" given the known efficacy and potential synergy of the two drugs used together. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012) (citations omitted); Ex. 1002 ¶¶ 95-96.

c. Concurrent administration of rituximab and CHOP would have been an obvious choice to a POSA.

Claim 11 also requires that the rituximab and CHOP be administered "concurrently." As explained above, "concurrently" means on the same day during the same hospital visit. *Supra* Part VII.D.

Although it would have been obvious to administer rituximab and CHOP 48 hours apart as in Link, it also would have been obvious based on the general knowledge of a POSA to administer rituximab and CHOP chemotherapy concurrently—that is, administer them to the patient on the same day and, in fact, to administer the infused drugs one immediately after the other—to maximize the amount of time the half-lives of the drugs overlapped. Ex. 1002 ¶ 100. Additionally, the general practice and knowledge of a POSA also would have made it obvious to administer the two drugs concurrently for the convenience to both doctors and patients by aligning treatments for fewer hospital visits. *Id.* ¶ 101.

Indeed, as Dr. Ozer explains, it was a general practice to try to reduce the number of outpatient visits because of the high cost associated with such visits to the patients. *Id.* For example, one reference from 1998 explained that "[a]mong less severely ill cancer patients, nonmedical costs of several thousand dollars per year are typical, with approximately 45% of nonmedical costs being for out-of-pocket expenditures such as transportation and food and 55% for lost wages." Ex. 1036, Bennett at 4. Another reference from 1984 showed that seven cycles of

chemotherapy every three weeks—which falls within the claimed methods—led to nonmedical costs to patients on the average of $1,151.99, with 43% being out-of-pocket expenses and 57% being lost wages. Ex. 1035, Houts at 4 ("A 21-week treatment regimen with treatments every 3 weeks would be calculated to cost $1151.99, 43% of which was out-of-pocket expenses, and 57% was wages lost."). This cost would have increased significantly with an additional outpatient visit for each cycle, and thus would have motivated a POSA to reduce the number of such visits. Ex. 1002 ¶ 101; *see also Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1127–28 (Fed. Cir. 2000) (finding "a motivation to combine" based cost consideration).

This need for convenience, itself, would have part of the general knowledge of a POSA and motivated a POSA to choose the same dosing cycle for rituximab as the chemotherapy cycle. *Cross Med. Prods., 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 quotation marks omitted); *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329 (Fed. Cir. 2014) ("A relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance."). No prior art taught away from, or otherwise discouraged, such a convenient, concurrent

administration. Ex. 1002 ¶ 101. Indeed, concurrent administration was one of a "finite number of identified, predictable" dosing options for using rituximab in combination with CHOP to achieve overlapping half-lives and thus the therapeutic benefit of the combination. *KSR*, 550 U.S. at 421; Ex. 1002 ¶ 102.

2. Claim 12 would have been obvious.

Claim 12, also an independent claim, is directed to "[a] method of treating a >60 year old diffuse large cell lymphoma patient comprising administering rituximab and CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient, wherein the rituximab is administered on Day 1 of each chemotherapy cycle and the CHOP is administered on Day 1 of each chemotherapy."

This claim would have been obvious over the same combination of references that would have made claim 11 obvious. The only difference between claim 12 and claim 11 is that claim 12 describes that rituximab and CHOP are both administered on "Day 1 of each chemotherapy cycle," whereas claim 11 describes that rituximab and CHOP are both administered "concurrently." When rituximab and CHOP are administered "concurrently" (i.e., on the same day), by definition, this includes co-administering these drugs—the only drugs in the treatment—on "Day 1" of the treatment cycle. Ex. 1002 ¶ 104. Therefore, claim 12 would have been obvious over the same combination of references as claim 11. *Id.*

3. Claim 15 would have been obvious.

Claim 15 specifies "[t]he method of claim 12 comprising six or eight chemotherapy cycles, wherein in each chemotherapy cycle a 375 mg/m^2 dose of rituximab is administered to the patient." This claim would have been obvious to a POSA over the same combinations references that would have rendered claims 11 and 12 obvious. Ex. 1002 ¶ 105. The only differences between claim 15 and claims 11 and 12 are that claim 15 also requires "six or eight chemotherapy cycles" and "a 375 mg/m^2 dose of rituximab" in each cycle. As explained above, however, it would have been obvious to add 375 mg/m^2 of rituximab to a mini-CHOP regimen (in six to eight cycles) as taught in Macedo in light of the teaching of Link that this rituximab dose in combination with full-dose CHOP potentially improved efficacy, but without adding toxicity. Similarly, it would have been obvious to add 375 mg/m^2 of rituximab to full-dose CHOP (also six to eight cycles) to treat patients who could withstand full-dose CHOP therapy. *See* Ex. 1004, Meyer 1995 at 7 (administering six to eight cycles of full-dose CHOP to patients over 65); Ex. 1002 ¶ 106 (Dr. Ozer administered eight doses of full-dose CHOP to DLCL patients over 60). By combining these teachings, a POSA would have arrived at the method of claim 15—375 mg/m^2 of rituximab in combination with CHOP (either mini-CHOP or full-CHOP) in six or eight cycles for DLCL patients over 60. Ex. 1002 ¶ 105.

4. Claim 16 would have been obvious.

Claim 16 describes "[t]he method of claim 15 comprising administering eight chemotherapy cycles, wherein in each chemotherapy cycle a 375 mg/m^2 dose of rituximab is administered to the patient." The only difference between claim 16 and claim 15 is that claim 16 specifies eight cycles of treatment out of the six or eight cycles described in claim 15. This claim would have been obvious over the same references that would have rendered claim 15 obvious to a POSA. Macedo taught up to eight cycles of mini-CHOP for DLCL patients over 60 and, as explained, it would have been obvious to add 375 mg/m^2 as in Link to this regimen because rituximab potentially increased efficacy without increasing toxicity. Thus, it would have been obvious for a POSA to combine these references to arrive at the method of claim 16. Ex. 1002 ¶ 106. It similarly would have been obvious to add rituximab to eight cycles of full-dose CHOP for those patients who could successfully withstand the toxicity of this more effective regimen. *Id.* (Dr. Ozer personally administered eight doses of full-dose CHOP to DLCL patients over 60); Ex. 1004, Meyer 1995 at 7 (administering six-to-eight cycles of full-dose CHOP to DLCL patients over 65); Ex. 1015, Miller at 4 (three patients over 65 successfully treated with eight cycles of full-dose CHOP).

B. Ground II: Claims 1-10 and 13-14 would have been obvious over Macedo, Meyer 1995, Link, Coiffier, and McNeil in view of Armitage and Maloney.

Claims 1-10 and 13-14 are generally directed to the same methods as claims 11-12 and 15-16, but with the addition of a transplantation regimen. These claims would have been obvious over the previous combination of references in view of Armitage and Maloney, which taught that bone marrow transplantation was an available therapy for DLCL patients over 60 and that transplantation could also be used in combination with rituximab. Ex. 1002 ¶ 107.

1. Claim 1 would have been obvious.

Claim 1 describes "[a] method of treating a >60 year old diffuse large cell lymphoma patient comprising administering anti-CD20 antibody and CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient, wherein the anti-CD20 antibody is administered to the patient in combination with a transplantation regimen." This claim would have been obvious to a POSA as of August 1999 over Macedo, Meyer 1995, Link, Coiffier, and McNeil, in view of Armitage and Maloney. Ex. 1002 ¶¶ 109-13.

As explained above with respect to claim 11, it would have been obvious to a POSA treating DLCL patients over 60 to add rituximab—which is an anti-CD20 antibody, Ex. 1005, Link at 7 (describing rituximab as a "monoclonal antibody that

targets the CD20 antigen")—either to a regimen of full-dose CHOP for patients requiring full-dose therapy and who could withstand the toxicity, or to a regimen of mini-CHOP for patients who could not withstand the toxicity of full-dose CHOP, to achieve better efficacy without additional toxicity. *See supra* Part IX.A.1. The only limitation in claim 1 not present in claim 11 is the addition of "in combination with a transplantation regimen." It would also have been obvious to a POSA to combine either the full-dose CHOP/rituximab or mini-CHOP/rituximab regimens discussed above with transplantation, as appropriate, in light of the teachings of Armitage and Maloney.

As previously explained, if initial treatments failed, a POSA knew that a patient could undergo high-dose chemotherapy that kills not only the cancerous cells, but also the healthy cells in the patient's bone marrow. Thus, before undergoing this high-dose therapy, the patient would have healthy cells collected for reinfusion after the high-dose therapy is completed. Ex. 1002 ¶ 110. Armitage taught that bone-marrow transplantation (BMT) can be used in elderly patients for this purpose: "Autologous BMT involves re-establishing hematopoietic cell function in patients after high-dose therapy for cancer" and it "can be performed in older patients with comparative safety." Ex. 1008, 5. Indeed, bone-marrow transplantation was acceptable for patients up to 70 years old. *Id.* at 6, Table 16-1. The specification echoes this prior art disclosure, conceding that "conventional

therapies" for patients with intermediate-grade lymphomas "have included chemotherapy and radiation, *possibly accompanied by either autologous or allogeneic bone marrow or stem cell transplantation*." Ex. 1001, 1:42-44 (emphasis added).

Armitage further taught that patients were "more likely to be cured when treated early in the course of disease at the time that the tumor remains sensitive to chemotherapy"; and, indeed, "a number of investigations have incorporated high-dose therapy and autologous BMT into the primary treatment of patients with intermediate- and high-grade [NHL]." Ex. 1008, 9. This suggested that if transplantation were necessary, it would be better to use this therapy in combination with chemotherapy such that the effects of chemotherapy and transplantation would overlap. Ex. 1002 ¶ 111.

Further, as explained in Part VII.A, "in combination with stem cell transplantation" includes the administration of rituximab at induction (before the actual transplantation of stem cells) along with a form of CHOP chemotherapy. Ex. 1002 ¶ 82. It would have been obvious to a POSA to use rituximab and full-dose or mini-CHOP at the induction phase of therapy, and to combine this regimen with a transplantation regimen if the patient insufficiently responded to this initial therapy. *Id.* ¶ 110. The Maloney reference further taught that rituximab could be used in combination with a transplantation regimen: "Since [rituximab] does not

appear to impair marrow reserves, it could possibly be used in patients who are myelosuppressed due to recent chemotherapy or following high-dose chemotherapy with ABMT [autologous bone marrow transplantation] or peripheral stem-cell rescue." Ex. 1009, 10. That is, rituximab did not negatively affect the cells needed for transplantation. Ex. 1002 ¶ 112; *see also* Ex. 1022, IPR2017-01168, Paper 6 at 11 ("On the current record, we discern no deficiency in Petitioner's characterization of [this teaching in Maloney],…or in Petitioner's assertions as to the reasonable inferences an ordinary artisan would make from [Maloney].").

Thus, claim 1 would have been obvious.

2. Claim 2 would have been obvious.

Claim 2 describes "[t]he method of claim 1, wherein the antibody comprises a chimeric anti-CD20 antibody." Rituximab is a chimeric-anti-CD20 antibody, *see* Ex. 1001, 3:67–4:3, and so this claim would have been obvious to a POSA over the same references that would have rendered claim 1 obvious. Ex. 1002 ¶ 114; *see also* Ex. 1005, Link at 7 (describing rituximab as a "chimeric" antibody that "targets the CD20 antigen").

3. Claim 3 would have been obvious.

Claim 3 describes "[t]he method of claim 2, wherein the antibody comprises rituximab." Because Link taught rituximab specifically, this claim would have been

obvious to a POSA over the same references that would have rendered claim 1 obvious. Ex. 1002 ¶ 115.

4. Claim 4 would have been obvious.

Claim 4 describes the method of claim 1, "wherein the lymphoma is accompanied by bone marrow involvement," i.e. with lymphocytes found in the bone marrow. This claim would have been obvious over the same combination of references as claims 1-3, because 43% of patients in the Coiffier study with bone marrow involvement effectively responded to the rituximab treatment. Ex. 1007, 3, Table 3. Maloney also would have rendered this claim obvious. Maloney disclosed that "[m]arrow involvement was present in 50% of patients" in its successful study of both low-grade and intermediate-grade NHL patients, Ex. 1009, 5, and further reported tumor responses "in peripheral blood, *bone marrow* (BM), spleen, bulky lymph nodes, and extranodal sites, and in patients who had relapsed following high-dose myeloablative chemotherapy." *Id.* at 3 (emphasis added); Ex. 1002 ¶ 116. But more fundamentally, as Dr. Ozer explains, there is nothing atypical about lymphoma accompanied by bone marrow involvement, and certainly nothing that requires unique treatment. Ex. 1002 ¶ 117.

5. Claim 5 would have been obvious.

Claim 5 describes "[t]he method of claim 1, wherein the transplantation regimen comprises bone marrow transplantation." As explained above, Armitage

taught that "[a]utologous BMT [bone marrow transplantation] involves re-establishing hematopoietic cell function in patients after high-dose therapy for cancer" and it "can be performed in older patients with comparative safety," and specifically was acceptable in patients up to 70 years old. Ex. 1008, 5, 6, Table 16-1. And Maloney taught that "[s]ince [rituximab] does not appear to impair marrow reserves, it could possibly be used in patients who are myelosuppressed due to recent chemotherapy or following high-dose chemotherapy with ABMT [autologous bone marrow transplantation] or peripheral stem-cell rescue." Ex. 1009, 10. It would have been obvious to a POSA to combine these teachings with the teachings of Macedo, Meyer 1995, Link, McNeil, and Coiffier and to add bone-marrow transplantation if a patient insufficiently responded to the initial rituximab/CHOP therapy. Ex. 1002 ¶ 119. Thus, this claim would have been obvious to a POSA over the same references that would have rendered claim 1 obvious.

6. Claims 6-10 would have been obvious.

Claim 6 describes "[t]he method of claim 1, wherein the anti-CD20 antibody and CHOP are administered simultaneously." The patent specification defines "simultaneous" to mean "either concurrently or during the same time period such that the circulating half-lives of the therapeutic agents overlaps." Ex. 1001, 3:41-44. As explained above with respect to claim 1, it would have been obvious to administer rituximab and full-dose or mini-CHOP concurrently to treat DLCL

patients over 60. *See supra* Part IX.A.1.c. Because the specification defines "simultaneous" to include "concurrently," claim 6 necessarily would have been obvious over the same combination of references that would have rendered claim 1 obvious. Ex. 1002 ¶ 120.

Claim 7 more specifically describes "[t]he method of claim 6, wherein the anti-CD20 antibody and CHOP are administered concurrently." As explained above with respect to claim 11, it would have been obvious to administer rituximab and CHOP concurrently to treat DLCL patients over 60. *See supra* Part IX.A.1.c. Thus, claim 7 would have been obvious over the same combination of references that would have rendered claim 1 obvious. Ex. 1002 ¶ 121.

Claim 8 describes "[t]he method of claim 7, wherein the antibody comprises rituximab." Because rituximab is an anti-CD20 antibody, claim 8 would have been obvious for the same reasons as claim 7. Ex. 1002 ¶ 122.

Claim 9 describes "[t]he method of claim 6, comprising administering the anti-CD20 antibody on Day 1 of each chemotherapy cycle and the CHOP on Day 1 of each chemotherapy cycle." Claim 10 describes "[t]he method of claim 9, wherein the antibody comprises rituximab." As previously explained, when rituximab and CHOP are administered "concurrently," by definition, the day on which CHOP and rituximab are administered is "Day 1" of the treatment cycle. *See supra* Parts VII.D,

IX.A.2. Therefore, claims 9 and 10 would have been obvious over the same combination of references as claims 7 and 8. Ex. 1002 ¶ 123.

7. Claim 13 would have been obvious.

Claim 13 describes "[t]he method of claim 9 comprising administering six or eight chemotherapy cycles, wherein in each chemotherapy cycle a 375 mg/m^2 dose of the anti-CD20 antibody is administered to each patient." The only difference between claim 13 and claim 15 is that claim 13 includes the limitation of claim 1 "in combination with a transplantation regimen." This claim would have been obvious for the same reasons as claim 15, in addition to the teachings of Armitage and Maloney, which taught a POSA that bone-marrow transplantation could be used in combination with initial therapies in DLCL patients over 60 if those initial therapies failed. *See supra* Part IX.B.1. Thus, this claim would have been obvious over the same references that rendered claim 15 obvious—Macedo, Meyer 1995, Link, McNeil, and Coiffier—in view of Armitage and Maloney. Ex. 1002 ¶ 124.

8. Claim 14 would have been obvious.

Claim 14 describes "[t]he method of claim 13 comprising administering eight chemotherapy cycles, wherein in each chemotherapy cycle a 375 mg/m^2 dose of the anti-CD20 antibody is administered to the patient." The only difference between claim 16 and claim 14 is that claim 14 includes the limitation of claim 1 "in combination with a transplantation regimen." But as explained with respect to claim

1, it would have been obvious to add a transplantation regimen to the method of claim 16 in view of Armitage and Maloney, which taught a POSA that bone-marrow transplantation could be used in combination with initial therapies in DLCL patients over 60 if those initial therapies failed. *See supra* Part IX.B.1. Thus, this claim would have been obvious over the same references that rendered claim 16 obvious—Macedo, Meyer 1995, Link, McNeil, and Coiffier—in view of Armitage and Maloney. Ex. 1002 ¶ 125.

C. Ground III: Claims 11-12 and 15-16 would have been obvious over Macedo, Meyer 1995, Link, and McNeil.

Additionally, claims 11-12 and 15-16 would have been obvious to a POSA entirely over references that qualify as prior art under both 35 U.S.C. § 102(a) and § 102(b): Macedo, Meyer 1995, Link, and McNeil. That is, the Board need not rely on Coiffier, which is only a § 102(a) reference, to find the claims obvious.

As explained, claims 11-12 and 15-16 are generally directed to treating DLCL[6] patients over 60 years old by concurrently administering 375 mg/m^2 of rituximab with CHOP chemotherapy (including mini-CHOP or full-dose CHOP) in six to eight cycles. Even without Coiffier's confirmation that rituximab was safe and effective in elderly patients, a POSA would have been motivated to combine

[6] All of the prior art references relied upon in Ground III and Ground IV studied Type G DLCL patients according to the IWF classification system.

rituximab with either full-dose CHOP or mini-CHOP in light of the motivation provided by McNeil to search for less toxic treatments for DLCL patients over 60, and the teaching of Link that adding rituximab to a full-dose CHOP regimen could potentially increase efficacy without increasing toxicity. Ex. 1002 ¶ 128. A POSA also would have reasonably expected success. *Id.*

Specifically, McNeil disclosed that "the search for other drug combinations that may be as effective but less toxic than CHOP continues," and that one such "alternative" to CHOP monotherapy in patients over 60 "could be CHOP plus the monoclonal antibody [rituximab]." Ex. 1006, 1-2. Given Link's teaching that 375 mg/m^2 rituximab combined with full-dose CHOP was at least as effective as full-dose CHOP alone, but also no more toxic, these prior art references would also have given a POSA a "finite number of identified, predictable solutions" to the known problem of treating DLCL patients over 60 more effectively without increasing toxicity—i.e., adding rituximab either to full-dose CHOP or to mini-CHOP. *KSR*, 550 U.S. at 421; Ex. 1002 ¶ 129. And McNeil's suggestion supplied a "clear motivation to combine." *Allergan, Inc.*, 726 F.3d at 1293. Moreover, it was obvious to combine rituximab and CHOP because they acted with separate and complementary mechanisms of action, as explained above. *See supra* Part IX.A.

In short, it would have been obvious to a POSA in view of solely § 102(b) art to add 375 mg/m^2 of rituximab either to the full-dose CHOP regimen (as in Link)

for patients who needed full-dose therapy but who could not withstand the toxicity, or to the mini-CHOP regimen of Macedo for patients who could not withstand the toxicity of full-dose CHOP. Ex. 1002 ¶ 128. In sum, claims 11-12 and 15-16 would have been obvious to a POSA over Macedo, Meyer 1995, Link, and McNeil.

D. Ground IV: Claims 1-10 and 13-14 would have been obvious over Macedo, Meyer 1995, Link, and McNeil in view of Armitage and Maloney.

Claims 1-10 and 13-14 are generally directed to the same methods as claims 11-12 and 15-16 but add the limitation of claim 1 "in combination with a transplantation regimen." Additionally, claim 4 adds the limitation "wherein the lymphoma is accompanied by bone marrow involvement." Even without Coiffier's confirmation that rituximab was safe and effective in elderly patients and its finding that 43% of patients with bone marrow involvement effectively responded to the rituximab treatment, these claims would have been obvious over entirely 35 U.S.C. § 102(b) prior art—Macedo, Meyer 1995, Link, and McNeil, in view of Armitage and Maloney.

For the same reasons explained above, the combined teachings of Macedo, Meyer 1995, Link, and McNeil would have motivated a POSA to add 375 mg/m^2 of rituximab either to full-dose CHOP or mini-CHOP in six-to-eight cycles with a reasonable expectation of success. Armitage would have then motivated a POSA to add a transplantation regimen to the methods of claims 11-12 and 15-16 for patients

not responding to the initial rituximab and CHOP combination therapy, for the reasons explained above in Part IX.B.1. Maloney also specifically recommended using rituximab, chemotherapy, and bone marrow transplantation: "Since [rituximab] does not appear to impair marrow reserves, it could possibly be used in patients who are myelosuppressed due to recent chemotherapy or following high-dose chemotherapy with ABMT [autologous bone marrow transplantation] or peripheral stem-cell rescue." Ex. 1009, 10.

Maloney also would have rendered claim 4 obvious to a POSA. As explained, claim 4 describes the method of claim 1, "wherein the lymphoma is accompanied by bone marrow involvement." Maloney disclosed that "[m]arrow involvement was present in 50% of patients" in its successful study of both low-grade and intermediate-grade NHL patients, Ex. 1009, 5, and further reported tumor responses "in peripheral blood, *bone marrow* (BM), spleen, bulky lymph nodes, and extranodal sites, and in patients who had relapsed following high-dose myeloablative chemotherapy." *Id.* at 3 (emphasis added); Ex. 1002 ¶ 132. But more fundamentally, as Dr. Ozer explains, there is nothing atypical about lymphoma accompanied by bone marrow involvement, and certainly nothing that requires unique treatment. Ex. 1002 ¶ 117.

In sum, claims 1-10 and 13-14 would have been obvious as of August 1999 over Macedo, Meyer 1995, Link, and McNeil, in view of Armitage and Maloney. *Id.* ¶ 132.

E. Patent Owner's rebuttal evidence and secondary considerations.

1. The prior art does not teach away from the claimed invention.

As explained in Part VI.C above, Patent Owner made a teaching-away argument during prosecution. Although not addressed by the Examiner, Petitioner addresses this argument out of an abundance of caution.

Patent Owner relied on Meyer 1998 and argued that "[e]ven using the standard dose" of CHOP in that study, in combination with an additional agent intended to reduce toxicity, "20% of patients" had "to stop therapy prematurely." Ex. 1028, 7. Because "even CHOP alone was thought to perhaps be too toxic for certain elderly patients," Patent Owner argued, the prior art thus allegedly taught away from the claimed invention. *Id.*

But Meyer 1998 does not teach away. "A reference does not teach away if it does not criticize, discredit, or otherwise discourage investigation into the invention claimed." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (ellipses and quote marks omitted). Meyer 1998 instead *encouraged* the use of standard doses of CHOP: "From these studies we conclude that, standard CHOP with [granulocyte colony stimulating factor to reduce toxicity] *can be safely given*

to elderly patients." Ex. 1020, 1 (emphasis added). To be sure, full-dose CHOP was too toxic for some (but certainly not all) elderly patients. But that fact supplied the motivation for a POSA to seek better treatments for such patients, such as combining rituximab and mini-CHOP.

2. There is no evidence of secondary considerations.

Patent Owner also briefly argued during prosecution that the 2014 Rituximab U.S. Prescribing Information showed an alleged surprising results—3.1 years of progression-free survival for DLCL patients over 60 on the rituximab-CHOP combination compared to 1.6 years on CHOP alone, and an overall survival at two years of 74% vs. 63%. Ex. 1026, 6. While the Examiner never addressed this argument, these results are nevertheless not surprising. As explained, it was already known in the prior art that rituximab combined with CHOP did not increase toxicity, but was likely more effective than CHOP alone. These subsequent studies merely confirmed what a POSA would have reasonably expected in 1999. Ex. 1002 ¶ 135. Additionally, the study referred to by Patent Owner during prosecution did not entail administration of rituximab and CHOP "concurrently" or with a transplantation regimen, and therefore any purported unexpected results would have no nexus to the claims requiring concurrent administration (claims 7-16) or transplantation (claims 1-10, 13-14). Ex. 1034, 25-26; Ex. 1002 ¶ 135; *In re Huai-Hung Kao*, 639 F.3d 1057, 1069 (Fed. Cir. 2011) ("in considering the evidence of unexpected

results . . . there must be a nexus to some aspect of the claim not already in the prior art").

Patent Owner's purported evidence of secondary considerations also cannot save the '744 patent 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). That is the situation here, as discussed above, even assuming Patent Owner's alleged secondary considerations are substantial (they are not).

Finally, 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 Petitioner 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 Patent Owner.

X. CONCLUSION

For the foregoing reasons, the Board should institute *inter partes* review and cancel claims 1-16 of the ’744 patent as unpatentable.

Dated: December 1, 2017

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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 13,998 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).

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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. 9,504,744 B2, and at another address known as likely to effect service, as follows:

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