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. IPR2017-01168
Patent 8,821,873 B2
Issued: September 2, 2014
Filed: October 3, 2013

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

PETITION FOR *INTER PARTES* REVIEW

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I. INTRODUCTION

Petitioner, Pfizer, Inc. requests *inter partes* review and cancellation of claims 1-5 of U.S. Patent No. 8,821,873 B2 ("the '873 patent"). These claims are generally 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. The '873 patent recites a method of treating [1] diffuse large B-cell lymphoma [2] in patients over 60 years old [3] by administering "CHOP" chemotherapy[1] and the monoclonal antibody rituximab, [4] in combination with peripheral stem cell transplantation. 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 (August 1999) in light of references never considered by the Examiner.

Indeed, the '873 patentees added nothing to the teachings of the prior art. They did not claim to have invented CHOP chemotherapy. They did not claim to have invented the monoclonal antibody rituximab. They also did not claim to have

[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, 8:37-44.

invented the method of stem cell transplantation to offset the toxic effects of CHOP chemotherapy. Nor did they even claim to have invented the method of using CHOP in combination with rituximab for patients over 60 with DLCL. Instead, the patentees merely claim 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 state of the art as of August 1999 was to use chemotherapy—preferably CHOP—as a first-line treatment for patients with DLCL. If the patients did not improve, or if the patients were at higher risk of failure altogether, high-dose chemotherapy was initiated. To offset the increased toxicity due to the higher doses of chemotherapy, patients would receive "autologous" stem cell transplantation, with stem cells from bone marrow furnishing them with healthy cells. As explained by the 1998 Moreau reference, "High-dose therapy with autologous stem cell transplantation (ASCT) may be considered *the treatment of choice* in patients with intermediate- or high-grade non-Hodgkin's lymphoma (NHL) who relapse after primary therapy." Ex. 1007, 1 (emphasis added).

However, patients over 60 were usually excluded from high-dose therapy, because they were more susceptible to the toxic effects of the chemotherapy. As Moreau explained: "ASCT is usually restricted to patients aged ≤60 years, partly due to the anticipated poor tolerance of intensive treatment in elderly patients." *Id.* The

1998 McNeil reference similarly noted that CHOP therapy was "markedly less successful in older patients," explaining that "CHOP, like some other chemotherapy regimens, is more toxic in this age group." Ex. 1003, 1. Thus, McNeil noted that, as of February 1998, doctors were still "looking for an alternative [to high-dose CHOP] for patients age 60 and above" with DLCL. *Id.* "[T]he search for other drug combinations that may be as effective but less toxic than CHOP continues." *Id.* at 2.

But McNeil suggested, and the Moreau reference confirmed, CHOP chemotherapy combined with stem cell transplantation from the *peripheral blood* (rather than the bone marrow) was effective and well tolerated by patients over 60. Importantly, neither of these references was before the Examiner.

As McNeil explained: "One more approach to NHL in the elderly involves peripheral stem cell transplants[,] an approach that is combined with low-dose chemotherapy regimens" such as CHOP. *Id.* (quoting Julie Vose, M.D.). "The idea is that stem cells from a sibling donor may induce a graft vs. tumor effect, i.e., the sibling stem cells will mount an immune response against the host cancer cells." *Id.* McNeil further reported that initial trials were showing "impressive responses." *Id.* (quoting Richard Champlain, M.D.).

The Moreau reference, published a few months later in June 1998, confirmed to those skilled in the art well before August 1999 that a reduced course of

CHOP chemotherapy in combination with peripheral stem cell transplantation could be used to treat patients over 60 years old with DLCL. In the Moreau study of patients aged 61-65, eight of whom had DLCL, the patients received three courses of CHOP chemotherapy followed by intensive therapy and peripheral blood stem cell transplantation ("PBSCT"). Seven out of the study's eight patients with DLCL had some response to initial CHOP chemotherapy, and half had a complete response to CHOP followed by the PBSCT. The study thus concluded "that PBSCT can probably be performed in patients between 61 and 65 years of age." Ex. 1007, Moreau at 3. Although Moreau reported success, half of the patients were not completely tumor-free after receiving this treatment regimen. *Id.* Thus, skilled artisans were motivated to improve the treatment taught in Moreau. Ex. 1002 ¶ 63.

The prior art further disclosed how to get such improvement for DLCL patients over 60: add the monoclonal antibody rituximab. By 1997, the U.S. Food and Drug Administration ("FDA") had 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. 1004, Rituxan™ label at 1; Ex. 1002 ¶ 46.

Just one month after the Moreau reference was published—in July 1998, more than a year and a half before the filing of the application for the '873 patent—the Link reference taught that using rituximab in combination with CHOP for the

treatment of intermediate- and high-grade B-cell lymphomas, including DLCL, was likely superior to, but no more toxic than, using CHOP alone. Link taught that the combination of CHOP and rituximab "represents a tolerable therapy with serious adverse events occurring with a *frequency similar* to that seen with conventional CHOP alone and may offer *higher response rates*." Ex. 1005, 5 (emphases added). In other words, the prior art taught that CHOP combined with rituximab was *at least as good as CHOP alone, and maybe better*—but without any risk of additional toxicity. Ex. 1002 ¶ 67.

In view of the ongoing clinical study of rituximab, McNeil specifically suggested combining rituximab with CHOP to improve treatment of patients over 60 who suffer from DLCL: "One alternative" to conventional CHOP therapy for patients over 60 "could be CHOP plus the monoclonal antibody [rituximab]." Ex. 1003, 1. Yet another reference, Maloney, recommended adding rituximab to chemotherapy and stem-cell transplantation regimens: "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." Ex. 1008, 10. Finally, the Coiffier reference, which studied rituximab specifically in patients over 60 years old with DLCL, 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. 1006, 1 (emphasis added).

As explained in the declaration of Dr. Howard Ozer, the Moreau and Link references in view of the motivation described in McNeil and Maloney would have motivated a POSA as of August 1999 to add rituximab to existing regimens involving CHOP, because the combination of CHOP and rituximab was more effective, but no more toxic, than CHOP alone. One of these obvious treatments included adding rituximab to the regimen disclosed in Moreau, i.e., CHOP and peripheral blood stem cell transplantation for patients over 60 years old with DLCL in order to obtain more effective results but without additional toxicity. Ex. 1002 ¶¶ 91-99. Alternatively, all the claims would be obvious over the combination of these references and the Coiffier reference.

This obvious treatment is what the patentee claimed as an invention in the '873 patent. Therefore, all claims of that patent should be canceled as obvious.

II. MANDATORY NOTICES

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

1. ***Real parties-in-interest.*** The real party in interest is Petitioner Pfizer, Inc. ("Pfizer" or "Petitioner"). No other parties exercised or could have exercised

control over this Petition; no other parties funded or directed this Petition. *See* Trial Practice Guide, 77 Fed. Reg. 48,759-60.

2. ***Related matters.*** The ’873 patent is not currently subject to any litigation to the best of Petitioner’s knowledge. Petitioner has also concurrently filed petitions for *inter partes* review of U.S. Patent No. 8,239,172 (IPR2017-01166) and No. 8,557,244 (IPR2017-01167). 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 experts (Drs. Ozer and Bennett). Of those other challenged patents, U.S. Patent No. 8,557,244 claims priority to the same application to which the ’873 patent claims priority.

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
- *Fax number*: (202) 282-5100

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 (i) the '873 patent is available for *inter partes* review; and (ii) Petitioner is not barred or estopped from requesting review of any claim of the '873 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 cancelation of claims 1-5 of the '873 patent pursuant to the following statement of the precise relief requested:

Ground	Claims	Basis	Reference(s)
I	1-5	§ 103(a)	Moreau (Ex. 1007); Link (Ex. 1005); McNeil (Ex. 1003); and Maloney (Ex. 1008)

II	1-5	§ 103(a)	Moreau (Ex. 1007); Maloney (Ex. 1008); Link (Ex. 1005); McNeil (Ex. 1003); and Coiffier (Ex. 1006)

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.

IV. LEVEL OF ORDINARY SKILL IN THE ART

The '873 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. Howard Ozer, use August 11, 1999, as the relevant date for analysis of the level of skill and knowledge of a person of ordinary skill in the art ("POSA"). Ex. 1002 ¶ 14. The arguments and analysis in this petition would not change if the critical date were August 11, 1998, one year before the priority date, because all prior art references relied on by Petitioner to support this petition (with one exception, Coiffier) were published before August 11, 1998.

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 '873 patent would include a practicing oncologist with at least an M.D. degree and several years of experience treating patients with NHL and/or researching treatments for NHL, including with chemotherapeutic drugs. Ex. 1002 ¶ 15.

V. THE PRIOR ART AND THE '873 PATENT

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

A. The specification concedes that CHOP chemotherapy and stem cell transplantation were "conventional therapies."

NHL is a cancer that targets the body's lymphatic system. Ex. 1002 ¶ 30. NHL is a type of B-cell lymphoma characterized by the uncontrollable growth of the body's B-cells. *Id.* B-cells are the body's white blood cells that distribute antibodies in the system when they grow into mature cells. They are also referred to as B lymphocytes. *Id.* ¶ 31. NHL manifests in different ways in different patients: "[N]on-Hodgkin's lymphomas constitute a heterogeneous group of neoplasms of the lymphoid system that include distinct entities defined by clinical histologic, immunologic, molecular, and genetic characteristics." Ex. 1015, Skarin at 1; *see* Ex. 1002 ¶ 31. The type of lymphoma is "the major determinant[] for treatment outcome and prognosis," because the different classifications of lymphoma respond differently to chemotherapy. Ex. 1011, Hiddemann II at 2; *See* Ex. 1002 ¶ 33.

One of the central determining factors for a patient's prognosis was (and remains) his or her grade of lymphoma: low-, intermediate-, or high-grade NHL.

Ex. 1002 ¶ 34. 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 II at 2-3; Ex. 1015, 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 III at 1; Ex. 1002 ¶ 35. These new classification systems helped skilled artisans "identify previously unrecognized entities with distinct histopathological and clinical features." Ex. 1012, Hiddemann III at 1; Ex. 1002 ¶ 35. They also helped skilled artisans "establish a proper diagnosis" and "estimate the prognostic relevance of this diagnosis" to make their "therapeutic decisions." Ex. 1012, Hiddemann III at 2-3. 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 II 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. 1015, Skarin at 1-3; Ex. 1001, 2:50-67. Lymphomas categorized as intermediate- or high-grade were often studied together, as treatments were considered to be the same. Ex. 1002 ¶ 35-37; *see also, e.g.*, Ex. 1006 (Coiffier) (studying four types of intermediate- or high-grade lymphomas); Ex. 1005 (Link) (studying types D, G, and H together). As explained by the Hiddemann III 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 ¶ 39.

Patients with intermediate- or high-grade NHL, such as DLCL, were treated with chemotherapy and radiation to induce the cancer into remission. Ex. 1013, Foon at 10-11. The chemotherapy and radiation treatments work to target and kill the cancerous tumor-ridden B-cells in the body. Ex. 1002 ¶ 37. As of mid-1997, the most favored combination of chemotherapy drugs—because of its low toxicity relative to other chemotherapy combinations at their effective dose levels—was a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone, commonly abbreviated as CHOP. "CHOP, because of its [comparatively] low toxicity and ease of administration, again has been considered the standard of care for advanced stage diffuse large B cell lymphoma . . . ." Ex. 1010, Martelli at 7. The conventional number of doses or "cycles" was six. *Id.* at 4, Table IV.

For patients not responding to conventional CHOP doses, a skilled artisan could initiate "[i]ntensification of treatment with high dose therapy followed by autologous bone marrow transplantation (ABMT) or peripheral stem cell transplantation (PSCT)" to compensate for the increased toxicity. *Id.* at 8; Ex. 1002 ¶ 43. As the Moreau reference from June 1998 explained: "High-dose therapy with autologous stem cell transplantation (ASCT) may be considered *the treatment of choice* in patients with intermediate- or high-grade non-Hodgkin's lymphoma

(NHL) who relapse after primary therapy." Moreau et al., "Peripheral Blood Stem Cell Transplantation as Front-line Therapy in Patients Aged 61 to 65 Years: A Pilot Study," Bone Marrow Transplantation, 21: 1193-1196 (1998), Ex. 1007, 1 (emphasis added). And McNeil—another prior art reference that the Examiner did not consider—reports a study that "confirms CHOP as the standard therapy for the elderly." Ex. 1003, 2.

The patentees conceded this state of the prior art in the '873 patent specification in the background section of their invention:

> Conventional 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 if a suitable don[o]r is available, and if the bone marrow contains too many tumor cells upon harvesting. While patients often respond to conventional therapies, they usually relapse within several months.

Ex. 1001, 1:40-46. In other words, stem cell transplantation and chemotherapy (such as CHOP) were "conventional."

B. Patients over 60 were at higher risk of toxicity and had poorer prognoses with these conventional therapies.

Although a regimen of high-dose therapy and transplantation was the "treatment of choice" for patients suffering from intermediate- or high-grade NHL, Moreau explained that "ASCT is usually restricted to patients aged <60 years, partly

due to the anticipated poor tolerance of intensive treatment in elderly patients." Ex. 1007, 1. Indeed, Martelli explained the greatest determinant of relative risk for lymphoma patients was (and remains) the age of the patient—with those 60 years or older at nearly double the risk of those under 60. Ex. 1010, 2, Table I. McNeil similarly taught that "treatment for intermediate grade lymphoma [e.g., DLCL]—common among elderly NHL patients—is markedly less successful in older patients. CHOP cures only about half as many elderly patients as younger patients." Ex. 1003, 1.

McNeil also explained why: "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." *Id.* Thus, "[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]." *Id.* (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.* "[T]he search for other drug combinations that may be as effective but less toxic than CHOP continues." *Id.* at 2.

C. McNeil suggested, and Moreau showed, that these conventional therapies could be used in patients over 60 with DLCL with fewer doses of CHOP and stem cells from the peripheral blood.

As of the mid-1990s, new treatment options were becoming available that reduced the risk of toxicity in elderly patients. One of these options was stem cell transplantation using stem cells from the peripheral blood, a treatment method often referred to as "peripheral blood stem cell transplantation" (previously defined as PBSCT). PBSCT is a type of autologous stem cell transplantation, but from the peripheral blood rather than from bone marrow.[2]

In February 1998, McNeil suggested that fewer cycles of CHOP chemotherapy (three cycles rather than the traditional six), combined with stem cell transplantation from the peripheral blood (rather than the bone marrow), was effective and well tolerated by patients over 60. "One more approach to NHL in the elderly involves peripheral stem cell transplants[,] an approach that is combined with low-dose chemotherapy regimens." Ex. 1003, 2 (quoting Julie Vose, M.D.). "The idea is that stem cells from a sibling donor may induce a graft vs. tumor effect, i.e., the sibling stem cells will mount an immune response against the host cancer cells."

[2] Autologous stem cell transplantation refers to the transplantation of stem cells from *either* the bone marrow, or the peripheral blood. Ex. 1002 ¶ 43.

Id. McNeil reported that initial trials with low-dose CHOP were showing "impressive responses." *Id.*

In June 1998, Moreau showed that the results of fewer cycles of CHOP in combination with PBSCT were, in fact, impressive. Moreau first explained that PBSCT had shown "marked reductions in treatment-related toxicity as compared to historical reports of autologous bone marrow transplantation (ABMT)," suggesting stem cell transplantation from the peripheral blood "may become applicable to a subgroup of patients currently excluded from such trials, ie patients aged 61–65 years." Ex. 1007, 1. Moreau further explained that determining whether this population could be effectively treated with chemotherapy and transplantation was "all the more important as the median age of patients with NHL ranges from 60 to 65 years, and age by itself is one of the most powerful prognostic factors in intermediate- and high-grade NHL." *Id.*

The Moreau study included only patients over 60, and only those who had intermediate- or high-grade NHL. That study included 8 patients specifically with DLCL type "G" lymphoma. Ex. 1007, 2, Table 1. The patients received CHOP chemotherapy, "which is considered the standard first-line treatment in high-grade NHL," but only three courses—that is, half the traditional number of cycles. *Id.* at 3. If their disease showed some response, the patients proceeded to peripheral blood stem cell transplantation and intensive therapy. *Id.* at 1-2. Moreau reported that

seven out of the eight patients with DLCL type G had some response to initial CHOP chemotherapy, and that half had a complete response to stem cell transplantation from the peripheral blood. *See id.* at 2, Table 1 and 3, Table 3. The study thus concluded "that PBSCT can probably be performed in patients between 61 and 65 years of age." *Id.* at 3.

Despite these positive results, there was still room for improvement. Only half of the elderly patients in the Moreau study with DLCL were completely tumor-free as a result of their CHOP and PBSCT regimen. Fortunately, by 1997, another therapy emerged that showed promise for increasing the effectiveness of the CHOP/PBSCT prior art treatment: the addition of a monoclonal antibody.

D. Link taught that adding rituximab to CHOP was more effective but no more toxic than CHOP alone.

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 ¶ 46. 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. 1004, Rituxan™ label at 1.

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. 1004, 1. As a monoclonal antibody, rituximab binds itself to the CD20 antigen found on B-cells, thereby 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." *Id.* 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." *Id.* The label explained that the CD20 antigen was "expressed >90% of B-cell non-Hodgkin's lymphomas." *Id.* 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 ¶ 47.

The FDA approved label did not report on studies of rituximab's efficacy in high grades of lymphoma, or when rituximab was used in combination with CHOP chemotherapy. But doctors quickly began prescribing rituximab "off label." For example, as confirmed by an abstract published by November 1998, Tsai et al. used rituximab in patients with DLCL after they received chemotherapy and PBSCT. Ex. 1022, 11. The median age of the patient population was 59 and included patients as

old as 62. Ex. 1022, 11. Six of the seven patients had complete or partial responses. *Id.* Tsai concluded: "Rituximab appears to have significant activity and is well tolerated in patients with progressive intermediate grade NHL after P[B]SCT." *Id.*

Tsai was hardly alone in experimenting with rituximab for off-label treatments. By July 1998, merely one month after the Moreau reference was published and over a year and a half before the date of the claimed invention, a study combining CHOP with rituximab in patients with intermediate- or high-grade lymphoma—21 of whom had diffuse large cell, type "G" lymphoma—was published. *See* Link et al., "Phase II Pilot Study of the Safety and Efficacy of Rituximab in Combination with CHOP Chemotherapy in Patients with Previously Untreated Intermediate- or High-Grade NHL," (May 1998) ("Link"), Ex. 1005, 5.

In this study of 31 patients (median age 49), patients were administered "rituximab 375 mg/m2 on day 1 of each 21 day cycle followed 48 [hours] later by CHOP." Ex. 1005, 5. The Link study included 21 patients diagnosed with type "G" DLCL. *Id.* Of the 33 patients in the study, 30 patients were evaluable for response. *Id.*; Ex. 1002 ¶ 66. 63% of the patients had complete responses, 33% of the patients had partial responses, and there was only one progression. Ex. 1005, Link at 5.

Critically, the study concluded that rituximab in combination with CHOP did not expose patients to greater levels of toxicity than they would have been previously exposed to using CHOP therapy alone. *See id.*; Ex. 1002 ¶ 67. Link taught that

"[t]his regimen [CHOP and rituximab] represents a tolerable therapy with serious adverse events occurring with a *frequency similar* to that seen with conventional CHOP alone and may offer *higher response rates*." Ex. 1005, 5 (emphases added); Ex. 1002 ¶ 67. The Examiner thus concluded that Link taught the "treatment of patients with untreated intermediate- or High-Grade NHL . . . comprising the administration of a combination of rituximab and CHOP therapy." Ex. 1019, 6; *see also* Ex. 1002 ¶ 67. The crucial teaching, however, was that adding rituximab to CHOP was *at least as effective as CHOP alone*, but it was no more toxic than CHOP. This suggested it could be used in patient populations at risk for unacceptable toxicity: those over 60 years old.

E. McNeil suggested combining rituximab and CHOP in elderly patients, and Maloney suggested combining rituximab with CHOP and stem cell transplantation.

Although Link did not study patients over 60, the increased effectiveness of rituximab and CHOP over CHOP alone, without any increase in toxicity, led those skilled in the art to recommend the CHOP/rituximab combination for elderly patients. As previously explained, McNeil, for example, taught that "[o]ne 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." Ex. 1003, 1; Ex. 1002 ¶¶ 56-58. Thus, "[w]e know from this prognostic index that we should be looking for an alternative [to CHOP monotherapy] for patients age 60 and above." Ex. 1003,

McNeil at 1 (quoting Thomas Habermann, M.D.); *see also id.* at 1-2; Ex. 1010, Martelli at 11-12; Ex. 1002 ¶ 57. Reporting on on-going clinical trials with rituximab, McNeil specifically suggested combining CHOP and rituximab in patients over 60: "[W]e should be looking for an alternative [NHL treatment] for patients age 60 and above" and "[o]ne alternative could be CHOP plus the monoclonal antibody [rituximab]." Ex. 1003, 1; Ex. 1002 ¶¶ 57-58.

Another prior art reference suggested combining rituximab not just with CHOP, as in Link and McNeil, but also with stem cell transplantation. *See* Maloney et al, "IDEC-C2B8: Results of a Phase I Multiple-Dose Trial in Patients With Relapsed Non-Hodgkin's Lymphoma," *Journal of Clinical Oncology* (Oct. 1997) ("Maloney"). Maloney studied rituximab in 20 patients with all grades of NHL who had relapsed after previous treatments. Ex. 1008, 3. As 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. Indeed, Maloney taught that "[r]esponses occurred in patients heavily pretreated with chemotherapy, including aggressive regimens and ABMT." *Id.*

Maloney also taught that rituximab was effective in lymphomas with bone marrow involvement, i.e. in which the bone marrow had cancerous cells. *Id.* at 3

("Tumor responses occurred in peripheral blood, bone marrow (BM), spleen, bulky lymph nodes, and extranodal sites, and in patients who had relapsed following high-dose myeloablative chemotherapy."). Indeed, "[m]arrow involvement was present in 50% of patients" in Maloney's successful study. *Id.* at 5. Other studies confirmed the utility of rituximab in elderly patients as well as in disease with bone marrow involvement.

F. Coiffier confirmed that rituximab was safe and effective in elderly patients with DLCL and suggested that it should be studied in combination with chemotherapy.

Another prior art reference specifically studied rituximab in patients over 60. Coiffier et al., "Rituximab (Anti-CD20 Monoclonal Antibody) for the Treatment of Patients With Relapsing or Refractory Aggressive Lymphoma: A Multicenter Phase II Study" (1998). Coiffier studied the effect of rituximab in 54 patients, but where 30 of those patients had DLCL. Ex. 1006, 2.

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. Of the patients who were diagnosed with DLCL, 37% of those patients responded to the rituximab treatment. *Id.* at 3.

Coiffier showed that rituximab was thus safe and efficacious in patients over 60 years old with DLCL. Ex. 1002 ¶ 74. Coiffier concluded: "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. 1006, 1.

Additionally, 43% of patients in the Coiffier study with bone marrow involvement effectively responded to the rituximab treatment. *Id.* at 3, Table 3. Thus, a POSA would know from this study that this was an effective treatment for elderly patients with bone marrow involvement. Ex. 1002 ¶ 75.

VI. PATENT CLAIMS, SPECIFICATION, AND FILE HISTORY

A. The '873 patent claims

The '873 patent claims the following:

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

B. The ’873 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. While patients often respond to conventional therapies, they usually relapse within several months.” Ex. 1001, 1:40-46. 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 5:66–6:2. Because patients can relapse after receiving conventional therapies, rituximab may be most beneficial to patients “who are refractory to other types of

treatments, or who have relapsed following other types of treatments, such as chemotherapy or radiotherapy," and it might "have a synergistic effect in decreasing the chance of relapse if administered in conjunction with other conventional therapies." *Id.* at 3:20-28.

The claimed invention includes "methods comprising the administration of rituximab and CHOP." A skilled artisan can use the claimed invention in any arrangement that is most beneficial to the patient. Indeed, "[d]epending on the particular patient, said chemotherapy may be administered simultaneously or sequentially in either order." *Id.* at 3:32-34. "'Simultaneously' means either concurrently or during the same time period such that the circulating half-lives of the therapeutic agents overlaps." *Id.* at 3:34-36.

The specification instructs a POSA "[w]hen there is bone marrow involvement," that 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 6:8, 6:13-17. "'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 6:17-20.

C. Prosecution history

The ’873 is a divisional application of U.S. Application No. 09/628,187 and was filed on July 28, 2000. As originally filed, claims 17-23 were directed toward the therapeutically effective treatment of intermediate- or high-grade lymphoma using an anti-CD20 antibody in combination with chemotherapy for patients who have stem cell transplantation. After a series of rejections and amendments over the course of several years, the patentees finally arrived at the current claim language. And while this Petition outlines new prior art references the Examiner did not consider during prosecution, the patent application’s last rejection is illustrative of the prior art considerations and claim rejections that are relevant for this petition.

On January 6, 2014, the Examiner rejected the claims (1-3, 6, and 7) of the application that the Examiner ultimately issued as the ’873 patent as anticipated over an article published by Tsai et al. (Ex. 1022). The Examiner concluded that “Tsai teaches a method of administering Rituximab to patients with diffuse large cell NHL to patients that had been treated with high dose chemotherapy and peripheral stem cell transplantation.” Ex. 1019, 4. Thus, claims relating to the use of an anti-CD20 antibody (rituximab) administered in combination with stem cell transplantation were rejected by the Examiner.

The Examiner rejected several of the claims (1-4 and 9) as obvious in light of articles published by Link (Ex. 1005) and Coiffier (Ex. 1006). The Examiner

concluded "[i]t would have been have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used the method of Link," comprising CHOP and rituximab, "to treat patients with diffuse large cell lymphoma, at an age greater than 60 years old, because Coiffier teaches that rituximab has low toxicity and significant activity." Ex. 1019, 6. Therefore, "[o]ne 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." *Id.* at 7. The Examiner recognized a reasonable expectation of success "because Link teaches that the toxicity of rituximab does not overlap with the toxicity of CHOP therapy." *Id.*

In response to this rejection, the patentees amended the claims by incorporating the rejected claims into the language of claim 1, which previously had recited only "[a] method of treating a patient with diffuse large cell lymphoma comprising administering anti-CD20 antibody and chemotherapy to the patient." Ex. 1020, 2. Specifically, the patentees added to claim 1 the language of previous claims 6 and 7[3]—which were rejected as anticipated by Tsai, but not as obvious over

[3] Claim 6 had recited: "The method of claim 1, wherein the anti-CD20 antibody is administered to the patient in combination with a transplantation regimen[,]" and

Link—to get over the Link rejection. *Id.* at 3. Then, the patentees added to claim 1 the language of the previous claim 4[4]—which was rejected over Link, but not over Tsai—to get over the Tsai-based rejection. *Id.* Thus, claim 1 as amended specified that the patient must be greater than 60 years old, that the chemotherapeutic agent was CHOP, and that the anti-CD20 antibody would be used in combination with the stem cell transplantation regimen. *Id.* at 2.

In other words, the patentees merely incorporated three previously rejected claims into claim 1. The Examiner conducted an interview with the patent owner on March 25, 2015, to discuss the amended claims. In light of the amendments, the Examiner allowed the claims and stated in total: "Reviewed amendment filed 2/24/2014, which obviates all rejections of record. Unless a new issue arises, the claims as filed on 2/24/2014 are free of the art and allowable." Ex. 1021, 4.

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claim 7 had recited: "The method of claim 6, wherein the transplantation regimen comprises stem cell transplantation." Ex. 1024, 15.

[4] Claim 4 had recited: "The method of claim 1, wherein the chemotherapy comprises CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone)." Ex. 1024, 15.

VII. CLAIM CONSTRUCTION

A. Plain and ordinary meaning

The terms of the ’873 patent should be given their broadest reasonable interpretation, which in this case is their plain and ordinary meaning. “Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification. The plain meaning of a term means the ordinary and customary meaning given to the term by those of ordinary skill in the art at the time of the invention.” Manual of Patent Examining Procedure § 2111.01. “[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc).

As explained in more detail by Dr. Ozer, claim 1 requires that the anti-CD20 antibody (e.g., rituximab) be administered “in combination with” stem cell transplantation. This includes 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 ¶¶ 24-28. 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, 6:13-17. And the next sentence of the specification 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, 6:17-20; *see also id.* at 6:20-72.

VIII. PRIOR ART STATUS

As shown below and in the Declaration of Petitioner's expert librarian, Dr. Scott Bennett (Ex. 1016), each of the five references that Petitioner relies upon for the grounds of unpatentability asserted in this Petition—Moreau (Ex. 1007); Link (Ex. 1005); McNeil (Ex. 1003); Maloney (Ex. 1008); and Coiffier (Ex. 1006)—as well as the Rituxan™ label (Ex. 1004) is a printed publication that was publicly accessible before August 11, 1999, and therefore qualifies as prior art to the '873 patent under 35 U.S.C. §§ 102(a) and 102(b). *See also 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).").

A. Moreau (Ex. 1007)

Moreau is an authentic copy of a research paper by P. Moreau published in the June 2, 1998 issue of *Bone Marrow Transplantation*. Ex. 1016 ¶¶ 37-41. Public records confirm that *Bone Marrow Transplantation* is a periodical that was first published in 1986 and is held by 289 libraries worldwide. *Id.* ¶ 42. *Bone Marrow*

Transplantation has long been cataloged or indexed in a meaningful way, including by subject matter. *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 Weston Library at the University of Wisconsin indicates that the June 2, 1998 issue of the *Bone Marrow Transplantation*, which contains Moreau, was processed by that library on July 2, 1998. *Id.* ¶ 43. This date stamp has the general appearance of date stamps that libraries have long affixed to periodicals in processing them, and there is no indication or reason to believe this date label was affixed by anyone other than library personnel, or on any date other than July 2, 1998. *Id.* Therefore, Moreau was available to the public before August 11, 1998. *Id.* ¶¶ 44-45.

Accordingly, Moreau is prior art to the ’873 patent as a publicly accessible printed publication under 35 U.S.C. § 102(b).

B. 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). Ex. 1016 ¶¶ 46-51. The teachings of Link entered the realm of public discourse at least as of May 1998, when it was presented at the 34th annual meeting of the American Society of Clinical

Oncology ("ASCO"). *Id.* ¶ 52. The attendees of the meeting included numerous oncologists with experience treating NHL patients. Ex. 1002 ¶ 65. Indeed, ASCO's annual meeting was well known to persons of ordinary skill as of August 1998, many of whom would have attended it in person. *Id.* Also, a copy of the Program Proceedings was distributed to each of the conference's attendees as part of the ASCO's usual practice. *Id.*

Public records indicate that the program proceedings of ASCO's meetings, including the Link excerpt, are held by 154 libraries worldwide, where they were cataloged and indexed by subject matter such that members of the public—including ordinarily skilled artisans exercising reasonable diligence—would have had no difficulty finding copies of the program proceedings. Ex. 1016 ¶ 54; *see In re Wyer*, 655 F.2d 221, 226 (C.C.P.A. 1981) (reference is publicly accessible as prior art where it is "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it") (quotation omitted).

In particular, Link includes a date stamp printed with the words: "BIOMEDICAL LIBRARY," "JUL 22 1998" and "UNIVERSITY OF CALIFORNIA LOS ANGELES." Ex. 1005, 2; Ex. 1016 ¶ 55. Based on 50 years of experience as a professional librarian, Dr. Bennett affirms that this date stamp has the general appearance of date stamps that libraries have long affixed to periodicals

and series publications, and there is no indication or reason to believe that the date stamp was affixed by anyone other than UCLA's library personnel, or on any date other than the stamped date of July 22, 1998. *Id.*

Therefore, Link was available to the public before August 11, 1998. *Id.* ¶¶ 56-57. Because of the importance of current awareness among medical researchers and because of the care that medical and other librarians use to provide timely access to series publications for readers in the field of medicine, Link was publicly accessible before the critical date. *Id.* ¶ 56 n.1; *see also In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986) (finding that, where only a reference's receipt date was available, affidavit regarding "general library procedure as to indexing, cataloging, and shelving . . . in estimating the time it would have taken to make the [reference] available to the interested public" was "competent . . . [and] persuasive evidence that the [reference] was accessible prior to the critical date" as a § 102(b) printed publication).

Accordingly, Link is prior art to the '873 patent as a publicly accessible printed publication under 35 U.S.C. § 102(b).

C. McNeil (Ex. 1003)

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*. Ex. 1016 ¶¶ 58-62. Public records confirm that the *Journal* is a periodical that was first published in 1940 and is held by 1,302 libraries worldwide. *Id.* ¶ 63. The *Journal*

has long been cataloged or indexed in a meaningful way, including by subject matter. *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 Illinois at Urbana-Champaign Library indicates that the February 18, 1998, issue of the *Journal of the National Cancer Institute*, which contains McNeil, was processed by that library on March 13, 1998. *Id.* ¶ 64. This date stamp has the general appearance of date stamps that libraries have long affixed to periodicals in processing them, and there is no indication or reason to believe this date label was affixed by anyone other than library personnel, or on any date other than March 13, 1998. *Id.* Therefore, McNeil was available to the public before August 11, 1998. *Id.* ¶¶ 65-66.

Accordingly, McNeil is prior art to the ’873 patent as a publicly accessible printed publication under 35 U.S.C. § 102(b).

D. Maloney (Ex. 1008)

Maloney is an authentic copy of a research paper by David Maloney published in the October 1997 issue of the *Journal of Clinical Oncology*. Ex. 1016 ¶¶ 67-71. Public records confirm that the *Journal* is a periodical that was first published in 1983 and is held by 778 libraries worldwide. *Id.* ¶ 72. The *Journal* has long been cataloged or indexed in a meaningful way, including by subject matter. *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 Weston Library at the University of Wisconsin indicates that the October 1997 issue of the *Journal of Clinical Oncology*, which contains Maloney, was processed by that library on October 14, 1997. *Id.* ¶ 73. This date stamp has the general appearance of date stamps that libraries have long affixed to periodicals in processing them, and there is no indication or reason to believe this date label was affixed by anyone other than library personnel, or on any date other than October 14, 1997. *Id.* Therefore, Maloney was available to the public before August 11, 1998. *Id.* ¶¶ 65-66.

Accordingly, Maloney is prior art to the ’873 patent as a publicly accessible printed publication under 35 U.S.C. § 102(b).

E. Coiffier (Ex. 1006)

Coiffier is an authentic copy of a news report by B. Coiffier published in the September 15, 1998 issue of *Blood*. Ex. 1016 ¶¶ 77-82. Public records confirm that the *Journal* is a periodical that was first published in 1946 and is held by 965 libraries worldwide. *Id.* ¶ 83. *Blood* has long been cataloged or indexed in a meaningful way, including by subject matter. *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 September 15, 1998, issue of *Blood*, which contains Coiffier, was processed by that library on September 15, 1998. *Id.* ¶ 84. This date stamp has the general appearance of date stamps that libraries have long affixed to periodicals in processing them, and there is no indication or reason to believe this date label was affixed by anyone other than library personnel, or on any date other than September 15, 1998. *Id.* Therefore, Coiffier was available to the public before August 11, 1999. *Id.* ¶¶ 86-87.

Accordingly, Coiffier is prior art to the '873 patent as a publicly accessible printed publication under 35 U.S.C. § 102(a).

F. Rituxan™ label (Ex. 1004)

The Rituxan™ label is a true and accurate copy of the original 1997 drug label for Rituxan™ that was approved by the FDA in November 1997. Ex. 1016 ¶¶ 80-84. As Dr. Bennett confirms, the Rituxan™ label is available today from the FDA's

website, which represents that it is the original approved label for Rituxan™ as of November 26, 1997. *Id.* ¶ 88-89.[5]

Furthermore, the well-known "Internet Archive" service shows that the Rituxan™ label was available on the website of Genentech, which markets Rituxan™, as of January 23, 1998. *Id.* ¶ 90. The Internet Archive is a non-profit digital library founded in 1996 that maintains an archive of webpages collected from the internet by automated "crawlers." *Id.* ¶¶ 26–27. The archived webpages are available for search and retrieval through an interface called the "Wayback Machine," which renders accurate snapshots of webpages as they existed at the time they were collected. *Id.* ¶¶ 26–30. Based on the Rituxan™ label's appearance in the Internet Archive as of January 23, 1998, it is clear that public internet search engines at the time would have been able to find and index the Rituxan™ label, and that a POSA exercising reasonable diligence and using typical internet search tools would have readily found a copy of it. *Id.* ¶ 90; *see also, e.g., IBM Corp. v. Intellectual Ventures II LLC,* No. IPR2015-00089, Paper 44 at 57 (PTAB Apr. 25, 2016) (relying on

[5] The Rituxan™ label as of November 1997 can be located by searching the *Drugs@FDA: FDA Approved Drug Products* database at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process.

"Wayback Machine evidence" to "determine that Petitioner has shown that [a reference] was publicly available").

Moreover, a paper by third-party researchers published in November 1998 lists the Rituxan™ label as a reference. Ex. 1016 ¶ 91. Given the time that is generally required to research and write a paper, to submit it and have it reviewed, and to have it published, the paper was reasonably in preparation prior to August 1998, which further confirms that the Rituxan™ label was accessible in the public domain and in use before that time. *Id.* ¶¶ 91-92.

In addition, the Rituxan™ label's authenticity is evident from the 1999 edition of the *Physician's Desk Reference*® ("PDR"), a well-known reference that reproduces drug labels in their entirety. Ex. 1023. The 1999 edition of the PDR (which was received by the National Library of Medicine on December 30, 1998, *see id.* at 2) contains the same labeling information as the Rituxan™ label. *Compare* Ex. 1004 *with* Ex. 1023, 6-11.

Accordingly, the Rituxan™ label is prior art to the '873 patent as a publicly accessible printed publication under 35 U.S.C. § 102(b).

IX. ANALYSIS OF GROUNDS FOR TRIAL

The '873 patent would have been obvious to a person of ordinary skill in the art. The typical practice for treating NHL patients with DLCL was to use chemotherapy, of which CHOP was the standard regimen. For patients with high

risk factors or whose disease progressed, high-dose chemotherapy was initiated along with stem cell transplantation in order to reduce the toxic effects of the high-dose therapy. Ex. 1002 ¶ 61. According to the prior art, "[h]igh-dose therapy with autologous stem cell transplantation (ASCT) may be considered the treatment of choice in patients with intermediate- or high-grade non-Hodgkin's lymphoma (NHL) who relapse after primary therapy." Ex. 1007, Moreau at 1.

The chance of successful treatment, however, was greatly reduced for patients over 60 years old due to the risk of toxicity. Moreau taught that fewer cycles of CHOP therapy in combination with stem cell transplantation from the peripheral blood was an improved treatment option for this patient population, but there was still a need for better outcomes. Thus, "the general problem that confronted the inventor before the invention was made," see *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006), was whether new therapies would have improved the prognosis for patients over 60 years old.

In light of that problem, a skilled artisan would have been motivated to add rituximab to the CHOP and PBSCT regimen disclosed by Moreau as effective for elderly patients with DLCL. Link taught that adding rituximab to CHOP was superior to CHOP, but did not increase toxicity over CHOP alone—thus motivating a POSA to combine rituximab with CHOP in elderly patients. *See* Ex. 1005, 5. That is, it would have been obvious to a POSA to add rituximab to a reduced CHOP

regimen—including one followed by PBSCT—to achieve the same efficacy as CHOP monotherapy but with less toxicity, or to add rituximab to the full number of CHOP cycles to achieve more efficacy without any added toxicity. Ex. 1002 ¶¶ 87-92.

The prior art also explicitly supplied the motivation to use these therapies in patients over 60 years old, repeatedly recommending that rituximab be added to existing regimens. McNeil suggested combining rituximab to CHOP for elderly patients, and Maloney suggested adding rituximab to chemotherapy and stem cell transplantation. Any or all of these references would have motivated a POSA to add rituximab to the regimen disclosed by Moreau, leading directly to the claimed invention. Ex. 1002 ¶¶ 90-92. These references gave a POSA a "finite number of identified, predictable solutions" to a known problem in the art—the problem treating DLCL patients over 60 years old more effectively without increasing toxicity. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). Indeed, a skilled artisan would have reasonably anticipated success in pursuing the therapy suggested by the prior art that ultimately became the claimed invention. *See In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). Ex. 1002 ¶ 89.

A. Ground 1: Claims 1–5 would have been obvious over Moreau and Link in view of McNeil and/or Maloney.

1. Claim 1 would have been obvious.

Claim 1 would have been obvious over Moreau and Link in view of McNeil and/or Maloney. This claim recites "[a] method of treating a patient with diffuse large cell lymphoma comprising administering anti-CD20 antibody and chemotherapy to the patient, wherein the patient is >60 years old, wherein the chemotherapy comprises CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone), and wherein the anti-CD20 antibody is administered to the patient in combination with stem cell transplantation regimen."

a. "A method of treating a patient with diffuse large cell lymphoma comprising administering . . . chemotherapy to the patient, wherein the patient is >60 years old, wherein the chemotherapy comprises CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone), . . . in combination with stem cell transplantation."

As an initial matter, the patent's specification explains under "background of the invention" that chemotherapy and stem cell transplantation were "conventional" therapies for the treatment of intermediate- and high-grade lymphomas:

> Conventional 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 if a suitable don[o]r is available, and if the bone marrow

> contains too many tumor cells upon harvesting. While patients often respond to conventional therapies, they usually relapse within several months.

Ex. 1001, 1:40-46.

In other words, traditional chemotherapy such as CHOP, followed by stem cell transplantation, were "conventional therapies," i.e., a part of the prior art. "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." *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1570 (Fed. Cir. 1988); *see also 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").

Moreau, which was not before the Examiner, disclosed these "conventional" therapies for use in patients over 60, and specifically discussed a reduced CHOP regimen in combination with PBSCT. Moreau showed that seven out of eight patients over the age of 60 with DLCL had some response to initial CHOP chemotherapy, and that four of these eight had a complete response following PBSCT. *See* Ex. 1007, 2, Table 1 and 3, Table 3. The study concluded that CHOP therapy and PBSCT "can probably be performed in patients between 61 and 65 years of age." *Id.* at 3. McNeil also reported that the approach involving "peripheral stem cell transplants . . . combined with low-dose chemotherapy regimens" were showing "impressive responses." Ex. 1003, 2.

Moreau thus taught all but one element—the addition of rituximab—of claim 1. Specifically, Moreau taught "[a] method of treating a patient with diffuse large cell lymphoma comprising administering . . . chemotherapy to the patient, wherein the patient is >60 years old, wherein the chemotherapy comprises CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone), . . . in combination with stem cell transplantation." Ex. 1001, 8:37-44.

b. "A method of treating a patient with diffuse large cell lymphoma comprising administering anti-CD20 antibody . . . wherein the anti-CD20 antibody is administered to the patient in combination with stem cell transplantation regimen."

The only missing claim element from Moreau—the addition of an anti-CD20 antibody like rituximab—would have been obvious to a skilled artisan at the time of the claimed invention. Ex. 1002 ¶¶ 89-92. Because only half of the DLCL patients in Moreau had complete responses to the CHOP and PBSCT regimen, a POSA would have been motivated to find treatments that increased efficacy, reduced toxicity, or did both. The prior art taught that adding rituximab to the treatment taught by Moreau would lead to such improved results.

Link would have motivated a POSA to combine rituximab to the regimen of CHOP and PBSCT disclosed in Moreau, because Link taught that CHOP in combination with rituximab is at least as effective as, but no more toxic than, CHOP

alone. Ex. 1002 ¶ 89. As discussed, Link studied the combined use of CHOP chemotherapy and rituximab in patients with intermediate- or high-grade lymphomas. Twenty-one of its 31 patients had type G DLCL. All but one of the 30 evaluable patients improved, thus teaching that CHOP in combination with rituximab successfully treats DLCL. Ex. 1005, Link at 5. Critically, Link further taught that adding rituximab to a regimen of CHOP is likely more effective than 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).

These two prior art references (Moreau and Link), when viewed together as of August 11, 1999, by a POSA, satisfy each and every limitation of claim 1. As explained, because CHOP therapy and stem cell transplantation in an elderly DLCL population was taught by Moreau, but additional improvements in treatment were still necessary because only half of these patients experienced complete responses, Link would have motivated a POSA to replace CHOP in Moreau with CHOP plus rituximab. Ex. 1002 ¶¶ 88-90. That is, it would have been obvious to a POSA to add rituximab to a reduced CHOP regimen to achieve the same efficacy as CHOP monotherapy but with less toxicity, or to add rituximab to the traditional number of CHOP cycles to achieve more efficacy without any added toxicity. Ex. 1002 ¶ 89.

Thus, the Examiner concluded that a POSA would have "a reasonable expectation of success" of adding rituximab to CHOP in elderly patients "because Link teaches that the toxicity of rituximab does not overlap with the toxicity of CHOP therapy." Ex. 1019, 7.

As explained by Dr. Ozer, because the specification defines "in combination with" to include the combination of CHOP and rituximab at "induction," i.e., at the initial stage of chemotherapy but before the initiation of stem cell transplantation, Moreau and Link, when read together, thus satisfy each limitation of claim 1. Ex. 1002 ¶¶ 24, 87-89.

c. Additional motivation to combine Moreau and Link

A skilled artisan's motivation in view of Link to combine rituximab to the CHOP regimen disclosed by Moreau was made explicit by both McNeil and Maloney. Ex. 1002 ¶¶ 90-93. McNeil explained there were poorer outcomes for elderly patients because of the toxic effects of chemotherapy: "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." Ex. 1003, 1. "Older 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]." *Id.* (brackets in original). Thus, "the search for other drug combinations that may be as effective but less toxic than CHOP continues." *Id.* at 2. McNeil suggested that one such "alternative" to CHOP

monotherapy in patients over 60 "could be CHOP plus the monoclonal antibody [rituximab]." *Id.* at 1.

In view of the suggestion in McNeil to combine CHOP with rituximab, a POSA would have found it obvious to combine the teachings of Link and Moreau. Ex. 1002 ¶ 91. That is, a POSA administering CHOP and PBSCT to elderly patients would have been motivated to replace CHOP in that regimen with CHOP plus the chimeric anti-CD20 monoclonal antibody rituximab, which could be more effective than CHOP alone without increasing toxicity. Ex. 1005, Link at 5. As explained previously, the Examiner similarly found that a POSA had a "reasonable expectation of success . . . because Link teaches that the toxicity of rituximab does not overlap with the toxicity of CHOP therapy." Ex. 1019, 7.

Maloney independently supplied a motivation to combine the teachings of Link and Moreau. Maloney studied the effect of rituximab in a variety of patient populations, and the authors concluded: "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." Ex. 1008, 10. Maloney further noted that patients treated with chemotherapy and stem cell transplantation tended to show more responses to rituximab. *Id.* Maloney therefore would have motivated a skilled artisan to add

rituximab to patients also receiving transplantation and CHOP chemotherapy—because rituximab, while attacking the cancer, does not negatively affect the cells needed for transplantation and may lead to higher responses in patients. Ex. 1002 ¶ 92.

Therefore, it would have been obvious to add the monoclonal antibody rituximab—which Maloney describes as an "anti-CD20 monoclonal antibody," Ex. 1008, 3—to the Moreau regimen in light of Maloney's suggestion to add rituximab to combinations of chemotherapy and PBSCT. When a prior art reference specifically suggests that a skilled artisan combine different therapies, that is a "clear motivation to combine." *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292-93 (Fed. Cir. 2013) (holding that prior art reference teaching a "fixed combination of timolol with an alpha$_2$-agonist" would improve treatment supplied a "clear motivation to combine" the two drugs).

Especially given Link's teaching that rituximab combined with CHOP was more effective than 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 years old more effectively without increasing toxicity. *KSR*, 550 U.S. at 421. A set of solutions is "obvious to try" where the prior art provides direction about "which parameters were critical" or "which of many possible choices is likely to be successful," and "finite" where the

prior art thereby reduces the options to a set that is "small or easily traversed." *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009) (internal quotation marks omitted). Here, the two parameters were well known—efficacy and toxicity—as were the available options: CHOP, rituximab, and stem cell transplantation. At the time, rituximab was the only available anti-CD20 monoclonal antibody. Ex. 1002 ¶¶ 45-46.

Additionally, it was obvious to combine rituximab, which destroys cancerous B-cells by attaching to the CD20 antigens expressed on those cells, and CHOP, a form of chemotherapy, because of their separate mechanisms of action. 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).

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

2. Claim 2 would have been obvious.

Claim 2 recites the method of claim 1, wherein the antibody comprises a *chimeric* anti-CD20 antibody. Specifically, claim 2 recites: "The method of claim 1, wherein the antibody comprises a chimeric anti-CD20 antibody." This claim is obvious over the same combination of references as claim 1, because Maloney describes rituximab as a "*chimeric* anti-CD20 monoclonal antibody." Ex. 1008, 3 (emphasis added).

3. Claim 3 would have been obvious.

Claim 3 recites: "The method of claim 2, wherein the antibody comprises rituximab." This claim is obvious over the same combination of references as claims 1 and 2, because Maloney recommended adding "rituximab" as the specific anti-CD20 monoclonal antibody to the regimen disclosed by Moreau. *Id.*; *see also* Ex. 1002 ¶ 95.

4. Claim 4 would have been obvious.

Claim 4 recites the method of claim 1, "wherein the lymphoma is accompanied by bone marrow involvement." This claim is obvious over the same combination of references as claims 1–3, because "[m]arrow involvement was present in 50% of patients" in Maloney's successful study, Ex. 1008, 5, and Maloney 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). Maloney thus taught

a POSA that adding rituximab to CHOP therapy could successfully treat patients with cancerous cells in the bone marrow. Ex. 1002 ¶¶ 96-98.

But more fundamentally, as Dr. Ozer explains, "it is not unusual to have bone marrow involvement in intermediate-grade lymphoma patients because it is part of the lymphatic system. Lymphocytes circulate in the blood, which supplies bone marrow. There is nothing atypical about lymphoma accompanied by bone marrow involvement, and certainly nothing that requires unique treatment." Ex. 1002 ¶ 97.

5. Claim 5 would have been obvious.

Independent claim 5 mirrors claim 1, but specifies rituximab as the anti-CD20 antibody. Specifically, claim 5 recites: "A method of treating a patient with diffuse large cell lymphoma comprising administering rituximab and CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) to the patient, in combination with stem cell transplantation, wherein the patient is >60 years old."

This claim is obvious over the same combination of references as claims 1–4, because Maloney recommended using rituximab in combination with chemotherapy and stem cell transplantation, Ex. 1008, 3, thereby motivating a POSA to add rituximab to the regimen of CHOP and PBSCT disclosed in Moreau. Ex. 1002 ¶¶ 92-99. And as explained by Dr. Ozer, "in combination with stem cell transplantation" includes the administration of rituximab at the induction of CHOP

chemotherapy, but before the actual transplantation of stem cells. Ex. 1002 ¶¶ 24-28. Thus, these references collectively teach every element of claim 5.

B. Ground 2: Claims 1–5 would have been obvious over Moreau and Link in view of McNeil and/or Maloney, in view of Coiffier.

As explained above, claim 4 recites the method of claim 1, "wherein the lymphoma is accompanied by bone marrow involvement." As explained above, claims 1-5 are obvious over the combination of Moreau, Maloney, Link, and McNeil. Claim 4 in particular is obvious in view of Maloney, because "[m]arrow involvement was present in 50% of patients" in Maloney's successful study, Ex. 1008, 5, and Maloney 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). Further, as explained by Dr. Ozer, "it is not unusual to have bone marrow involvement in intermediate-grade lymphoma patients because it is part of the lymphatic system. Lymphocytes circulate in the blood, which supplies bone marrow. There is nothing atypical about lymphoma accompanied by bone marrow involvement, and certainly nothing that requires unique treatment." Ex. 1002 ¶ 97.

However, to the extent claim 4 is not obvious in light of the combination of references discussed above, it is independently obvious over the Coiffier reference in combination with those other references, because Coiffier disclosed that rituximab

successfully treated 43%—nearly half—of intermediate-grade patients with bone marrow involvement. *See* Ex. 1006, 3, Table 3; Ex. 1002 ¶¶ 100-101.

C. There is no evidence of secondary considerations.

The patentees did not rely on any evidence of secondary considerations to support their application, and Petitioner is aware of none. Even if there were secondary considerations, however, that would not render this patent nonobvious because even "substantial evidence" of secondary considerations is insufficient to "overcome the clear and convincing evidence that the subject matter sought to be patented is obvious." *Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d 1476, 1484 (Fed. Cir. 1997).

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

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

X. CONCLUSION

For the foregoing reasons, the Board should institute *inter partes* review and cancel claims 1-5 of the ’873 patent as unpatentable.

Dated: April 28, 2017

Respectfully submitted,

WINSTON & STRAWN LLP
1700 K Street NW
Washington, DC 20006
Telephone: 202-282-5000
Fax: 202-282-5100
Email: rituximabIPR@winston.com

/s/Jovial Wong
Jovial Wong
Reg. No. 60,115

Lead Counsel for Petitioner

Charles B. Klein
(to seek *pro hac vice* admission)
Eimeric Reig-Plessis
(to seek *pro hac vice* admission)

Back-Up Counsel for Petitioner

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 11,575 words (as calculated by the word processing system used to prepare the Petition), excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

Dated: April 28, 2017

Respectfully submitted,

WINSTON & STRAWN LLP
1700 K Street NW
Washington, DC 20006
Telephone: 202-282-5000
Fax: 202-282-5100
Email: rituximabIPR@winston.com

/s/Jovial Wong
Jovial Wong
Reg. No. 60,115

Lead Counsel for Petitioner

CERTIFICATE OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I certify that, on April 28, 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. 8,821,873 B2, and at another address known as likely to effect service, as follows:

ARNOLD & PORTER KAYE SCHOLER LLP
Three Embarcadero Center, 10th Floor
San Francisco, CA 94111

Michael R. Fleming (Reg. No. 67,933)
IRELL & MANELLA LLP
1800 Avenue of the Stars, Suite 900
Los Angeles, CA 90067

Dated: April 28, 2017

Respectfully submitted,

WINSTON & STRAWN LLP
1700 K Street NW
Washington, DC 20006
Telephone: 202-282-5000
Fax: 202-282-5100
Email: rituximabIPR@winston.com

/s/Jovial Wong
Jovial Wong
Reg. No. 60,115

Lead Counsel for Petitioner