

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. IPR2017-01167

Patent No. 8,557,244 B1

Issued: October 15, 2013

Filed: July 28, 2000

Title: TREATMENT OF AGGRESSIVE NON-HODGKIN'S LYMPHOMA  
WITH ANTI-CD20 ANTIBODY

---

**PETITION FOR *INTER PARTES* REVIEW**

***Mail Stop PATENT BOARD***

Patent Trial and Appeal Board

United States Patent and Trademark Office

P.O. Box 1450

Alexandria, VA 22313-1450

## TABLE OF CONTENTS

	<u>Page</u>
TABLE OF AUTHORITIES .....	v
LIST OF EXHIBITS.....	viii
I. INTRODUCTION .....	1
II. MANDATORY NOTICES .....	4
III. REQUIREMENTS FOR REVIEW.....	6
IV. LEVEL OF ORDINARY SKILL IN THE ART .....	6
V. THE PRIOR ART AND THE '244 PATENT .....	7
A. CHOP chemotherapy was the standard of care for patients with DLCL.....	8
B. Shipp taught that CHOP therapy was an effective treatment for patients with intermediate- and high-grade NHL accompanied by bulky disease. ....	12
C. McNeil and other prior art taught that older patients were still at risk of toxicity from CHOP chemotherapy. ....	16
D. McNeil suggested, and Link confirmed, that the combination of rituximab and CHOP was likely more effective, but no more toxic, than CHOP alone for DLCL patients—including patients above 60 years old.....	18
E. Coiffier confirmed that rituximab is effective with minimal toxicity in elderly patients with intermediate grades of NHL and in bulky disease. ....	21
VI. THE '244 PATENT CLAIMS, SPECIFICATION, AND PROSECUTION HISTORY .....	22
A. The Patent Specification.....	23
B. Prosecution History .....	24
VII. CLAIM CONSTRUCTION .....	26

A.	Plain and Ordinary Meaning .....	26
VIII.	PRIOR ART STATUS OF CITED REFERENCES .....	27
A.	Shipp (Ex. 1009).....	27
B.	McNeil (Ex. 1003).....	28
C.	Link (Ex. 1005) .....	29
D.	Coiffier (Ex. 1006) .....	31
E.	Rituxan™ label (Ex. 1004) .....	32
IX.	ANALYSIS OF GROUNDS FOR TRIAL .....	34
A.	Ground 1: Claims 1-2 would have been obvious over Shipp and Link in view of McNeil.....	36
1.	Claim 1 would have been obvious.....	36
a.	“A method of treating a patient with diffuse large cell lymphoma comprising administering . . . CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient, wherein the patient . . . has bulky disease (tumor > 10 cm in diameter).” .....	36
b.	“wherein the patient is > 60 years old” .....	38
c.	“comprising administering an unlabeled chimeric anti-CD20 antibody and” .....	39
d.	Motivation to combine.....	41
2.	Claim 2 would have been obvious.....	44
B.	Ground 2: Claims 1-2 would have been obvious over Shipp and Coiffier .....	44
1.	Claim 1 would have been obvious.....	44
a.	“A method of treating a patient with diffuse large cell lymphoma comprising administering . . . CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin,	

vincristine, and prednisone/prednisolone) chemotherapy to the patient, wherein the patient is > 60 years old and has bulky disease (tumor > 10 cm in diameter).”	44
b. “comprising administering an unlabeled chimeric anti-CD20 antibody and”	45
c. There was no teaching away.	46
2. Claim 2 would have been obvious.	49
C. There is no evidence of secondary considerations.	49
X. CONCLUSION.	50

## TABLE OF AUTHORITIES

	Page(s)
<b>Cases</b>	
<i>Allergan, Inc. v. Sandoz Inc.</i> , 726 F.3d 1286 (Fed. Cir. 2013) .....	42
<i>Ariosa Diagnostics v. Verinata Health, Inc.</i> , 805 F.3d 1359 (Fed. Cir. 2015) .....	7
<i>Bayer Schering Pharma AG v. Barr Labs., Inc.</i> , 575 F.3d 1341 (Fed. Cir. 2009) .....	43
<i>Constant v. Advanced Micro-Devices, Inc.</i> , 848 F.2d 1560 (Fed. Cir. 1988) .....	37
<i>In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.</i> , 676 F.3d 1063 (Fed. Cir. 2012) .....	43
<i>Galderma Labs., L.P. v. Tolmar, Inc.</i> , 737 F.3d 731 (Fed. Cir. 2013) .....	47
<i>In re Hall</i> , 781 F.2d 897 (Fed. Cir. 1986) .....	31
<i>IBM Corp. v. Intellectual Ventures II LLC</i> , No. IPR2015-00089, Paper 44 (PTAB Apr. 25, 2016) .....	33
<i>In re Kahn</i> , 441 F.3d 977 (Fed. Cir. 2011) .....	35
<i>In re Klopfenstein</i> , 380 F.3d 1345 (Fed. Cir. 2004) .....	27
<i>KSR Int’l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007).....	35, 43
<i>Mylan Pharm. Inc. v. Allergan, Inc.</i> , IPR2016-01127, Paper 8 (PTAB Dec. 8, 2016) .....	50

<i>Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.</i> , 719 F.3d 1346 (Fed. Cir. 2013) .....	43
<i>In re O’Farrell</i> , 853 F.2d 894 (Fed. Cir. 1988) .....	36
<i>Petroleum Geo-Services, Inc. v. WesternGeco LLC</i> , IPR2014-01478, Paper 18 (PTAB Mar. 17, 2015) .....	50
<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303 (Fed. Cir. 2005) (en banc) .....	27
<i>Richardson-Vicks, Inc. v. Upjohn Co.</i> , 122 F.3d 1476 (Fed. Cir. 1997) .....	50
<i>Sega of Am., Inc. v. Uniloc USA, Inc.</i> , IPR2014-01453, Paper 11 (PTAB Mar. 10, 2015) .....	50
<i>In re Wyer</i> , 655 F.2d 221 (C.C.P.A. 1981) .....	30
<i>Ex Parte Xintian E. Lin &amp; Qinghua Li</i> , 2016 WL 6560248 (PTAB, Nov. 2, 2016) .....	37
<b>Statutes</b>	
35 U.S.C. § 102(a) .....	27, 32
35 U.S.C. § 102(b) .....	<i>passim</i>
35 U.S.C. § 103(a) .....	6
<b>Other Authorities</b>	
37 C.F.R. § 42.8(b) .....	4
37 C.F.R. § 42.22(a)(1) .....	6
37 C.F.R. § 42.22(a)(2) .....	6
37 C.F.R. § 42.104 .....	6
37 C.F.R. § 42.104(b) .....	6

77 Fed. Reg. 48,759-60 .....4  
Manual of Patent Examining Procedure § 2111.01 .....27

## LIST OF EXHIBITS

Exhibit	Description
1001	White et al., U.S. Patent No. 8,557,244 B1, “Treatment of Aggressive Non-Hodgkin’s Lymphoma with Anti-CD20 Antibody (issued Oct. 15, 2013) (“the ’244 patent”)
1002	Declaration of Howard Ozer, M.D., Ph.D. in Support of Petition for <i>Inter Partes</i> Review
1003	Caroline McNeil, “Non-Hodgkin’s Lymphoma Trials In Elderly Look Beyond CHOP,” <i>J. Nat’l Cancer Inst.</i> , 90(4):266-67 (Feb. 18, 1998) (“McNeil”)
1004	Rituxan™ (rituximab) labeling (Nov. 1997) (“Rituxan™ label”)
1005	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,” <i>American Society of Clinical Oncology, Program/Proceedings, Thirty-Fourth Annual Meeting</i> , (May 1998) (“Link”)
1006	Coiffier et al., “Rituximab (Anti-CD20 Monoclonal Antibody) for the Treatment of Patients with Relapsing or Refractory Aggressive Lymphoma: A multicenter Phase II Study,” <i>Blood</i> , 92(6):1927-1932 (1998) (“Coiffier”)
1007	Davis et al., “Rituximab: First Report of a Phase II (PII) Trial in NHL Patients (pts) with Bulky Disease,” <i>Blood</i> , 92(10 suppl 1):414a (1998) (“Davis”)
1008	James O. Armitage & Dennis D. Weisenburger, “New Approach to Classifying Non-Hodgkin’s Lymphomas: Clinical Features of the Major Histologic Subtypes,” <i>J. Clin. Oncol.</i> , 16(8):2780-2795 (1998) (“Armitage II”)
1009	Shipp et al., “High-Dose CHOP as Initial Therapy for Patients with Poor-Prognosis Aggressive Non-Hodgkin’s Lymphoma: A Dose-Finding Pilot Study,” <i>J. Clin. Oncol.</i> , 13(12):2916-2923 (1995) (“Shipp”)

<b>1010</b>	Martelli et al., “Current Guidelines for the Management of Aggressive Non-Hodgkin’s Lymphoma,” <i>Drugs</i> , 53(6):957-972 (1997) (“Martelli”)
<b>1011</b>	W. Hiddemann, “Non-Hodgkin’s Lymphoma—Current Status of Therapy and Future Perspectives,” <i>Eur. J. Cancer</i> , 31A:2141-2145 (1995) (“Hiddemann II”)
<b>1012</b>	Hiddemann et al. “Lymphoma Classification—The Gap Between Biology and Clinical Management is Closing,” <i>Blood</i> , 88(11):4085-4089 (1996) (“Hiddemann III”)
<b>1013</b>	Kenneth A. Foon & Richard I. Fisher, “Lymphomas,” <i>Hematology</i> , 5th Ed. (1995), 1076-1096 (“Foon”)
<b>1014</b>	Michael J. Campbell & John E. Niederhuber, “B-Lymphocyte Responses,” <i>Clinical Oncology</i> , Abeloff et al., Eds. (1995), 100-126 (“Campbell”)
<b>1015</b>	Arthur T. Skarin & David M. Dorfman, “Non-Hodgkin’s Lymphomas: Current Classification and Management,” <i>CA Cancer J. Clinicians</i> , 47(6):351-372 (1997) (“Skarin”)
<b>1016</b>	Declaration of Scott Bennett, Ph.D.
<b>1017</b>	Michael L. Grossbard et al., “Monoclonal Antibody-Based Therapies of Leukemia and Lymphoma,” <i>Blood</i> , 80(4):863-878 (1992) (“Grossbard”)
<b>1018</b>	James O. Armitage et al., “Bone Marrow Transplantation,” <i>Clinical Oncology</i> , Abeloff et al., Eds. (1995), 295-305 (“Armitage I”)
<b>1019</b>	U.S. Application No. 60/148,286, Non-Final Office Action (dated June 26, 2012)
<b>1020</b>	U.S. Application No. 60/148,286, Amendment in Response to Non-Final Action (dated Aug. 20, 2012)
<b>1021</b>	U.S. Application No. 60/148,286, Notice of Allowability (dated Nov. 7, 2012)
<b>1022</b>	Tsai et al., “Progressive Intermediate Grade Non-Hodgkin’s Lymphoma After High Dose Therapy and Autologous Peripheral Stem Cell Transplantation (PSCT) Has a High Response Rate to Rituximab,” <i>Blood</i> , 92(10 Suppl. 1):415a (1998) (“Tsai”)

<b>1023</b>	Physicians' Desk Reference® (53rd ed. 1999) (excerpted), "Rituxan™ (Rituximab)"
-------------	---

## I. INTRODUCTION

Petitioner, Pfizer, Inc. requests *inter partes* review and cancellation of claims 1-2 of U.S. Patent No. 8,557,244 B1 (“the ’244 patent”). This patent recites a method of treating a patient [1] with diffuse large B-cell lymphoma (“DLCL”), a type of non-Hodgkin’s lymphoma (“NHL”), by [2] administering the monoclonal antibody rituximab and [3] chemotherapy known as “CHOP,”<sup>1</sup> [4] where the patient is over 60 years old and [5] has bulky disease (at least 1 tumor > 10 cm in diameter). Both claims of the ’244 patent would have been obvious to a person of ordinary skill in the art (“POSA”).

Indeed, the listed inventors for the ’244 patent added nothing to the teachings of the prior art. They did not claim to have invented the monoclonal antibody rituximab. They did not claim to have invented CHOP chemotherapy. They did not claim to have invented the method of using CHOP in combination with rituximab for patients over 60 with DLCL. Nor did they discover that CHOP chemotherapy treated patients with bulky disease. Instead, the applicants merely claimed to have

---

<sup>1</sup> 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<sup>®</sup>), Oncovin<sup>®</sup> (or vincristine), and prednisone (or prednisolone). Ex. 1002 ¶ 1 n.1; Ex. 1001, 8:41-47.

been the first to combine these prior art teachings. But such combination therapy 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 the patent's priority date, August 11, 1999, was to use chemotherapy—the most preferred of which was the CHOP drug combination—as a first-line treatment for patients with DLCL, including those over 60 and whose DLCL was accompanied by bulky disease. Ex. 1009, Shipp at 1; Ex. 1010, Martelli at 7, 10-11. If the patients did not improve or were at a higher risk of failure (particularly patients over 60 and/or with bulky disease), high-dose chemotherapy (such as a high-dose CHOP regimen) could be initiated. Ex. 1003, McNeil at 1; Ex. 1009, Shipp at 1. As explained by the Shipp reference published in 1995, “patients who are less likely to benefit from standard therapy may have a high [complete response] rate with the high-dose CHOP regimen.” Ex. 1009, 7.

But improved therapy for elderly DLCL patients, particularly those with bulky disease, was needed. According to a prior art reference from 1998 (McNeil), elderly patients had poorer prognoses because they could not tolerate chemotherapy as well as younger patients. Ex. 1003, 1. As McNeil explained, “CHOP cures only about half as many elderly patients as younger patients.” *Id.* The problem of treating elderly patients was particularly acute if they had bulky disease, because, as Shipp taught, “the subset of patients with bulky [disease] ([tumor]  $\geq 10$  cm)” was “unlikely

to be cured with standard therapy” (e.g., with standard doses of CHOP). Ex. 1009 at 1.

Fortunately, an improved treatment for elderly DLCL patients became available and was disclosed in the art before 1999: the combination of CHOP with the monoclonal antibody rituximab. In 1997, the antibody rituximab (Rituxan™) was approved by the U.S. Food and Drug Administration (“FDA”) for the treatment of low-grade B-cell NHL. Rituximab “binds specifically to the antigen CD20” that is “expressed on >90% of B-cell non-Hodgkin’s lymphomas,” and induces the death of those cells. Ex. 1004, Rituxan™ label at 1.

By 1998, more than a year and a half before the filing of the application for the ’244 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 events occurring with a *frequency similar* to that seen with conventional CHOP alone and may offer *higher response rates*.” Ex. 1005, 5 (emphases added). Indeed, even before the results of Link were published, McNeil had already suggested combining rituximab with CHOP to improve treatment of patients over 60 who suffered from intermediate-grade NHL—teaching that “[o]ne alternative” to conventional CHOP therapy in this elderly population “could be

CHOP plus the monoclonal antibody [rituximab].” Ex. 1003, 1. The Coiffier reference further taught that rituximab was effective in elderly patients with minimal toxicity, and in treating smaller tumors in patients with bulky disease. Ex. 1006, 3, Table 3.

As explained in the declaration of Dr. Howard Ozer (Ex. 1002), the combination of Shipp and Link in view of McNeil—or, independently, the combination of Shipp and Coiffier—would have motivated a POSA to add rituximab to standard-of-care CHOP therapy for patients over 60 years old with DLCL accompanied by bulky disease. Such a POSA would have had a reasonable expectation that such combination therapy with rituximab would be more effective than CHOP alone with no additional toxicity. The claimed invention is thus invalid as obvious.

## II. MANDATORY NOTICES

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

1. ***Real parties-in-interest.*** Pfizer, Inc. (“Pfizer” or “Petitioner”) is the real party-in-interest. 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 ’244 patent is currently being challenged by a different petitioner in *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01094. The grounds

of unpatentability asserted in IPR2017-01094 are not the same as the grounds asserted by Petitioner here, and this petition also includes prior art (e.g., Shipp) not relied upon by the petitioners in the *Celltrion* petition.

Petitioner has previously filed a petition for *inter partes* review of U.S. Patent No. 8,239,172 (IPR2017-01166). The patent challenged in that petition is owned by Patent Owner here and claims methods of using chemotherapy and rituximab to treat NHL. This previous petition and the current petition rely on overlapping prior art references and the same experts (Drs. Ozer and Bennett).

**3. *Lead and back-up counsel.*** Petitioner 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

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 '244 patent is available for *inter partes* review; and (ii) Petitioner is not barred or estopped from requesting review of any claim of the '244 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 1-2 of the '244 patent pursuant to the following statement of the precise relief requested:

Ground	Claims	Basis	Reference(s)
I	1-2	§ 103(a)	Shipp (Ex. 1009); McNeil (Ex. 1003); and Link (Ex. 1005)
II	1-2	§ 103(a)	Shipp (Ex. 1009) 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 '244 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 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 ground one of 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 '244 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 '244 PATENT**

In summarizing the state of the art as of August 1999, Petitioner cites additional references beyond the “prior art presented as the basis for obviousness,” because these references “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. CHOP chemotherapy was the standard of care for patients with DLCL.**

NHL is a cancer that targets the body's lymphatic system, characterized by the uncontrollable growth of the body's B-cells. Ex. 1002 ¶ 25. B-cells (sometimes called B lymphocytes) are white blood cells that, once matured, distribute antibodies in the human body. Ex. 1002 ¶ 27. 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; Ex. 1002 ¶ 28. 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 1-2; Ex. 1002 ¶ 28.

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 ¶ 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 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

¶ 30. 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 ¶ 30. The classification systems help 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) Follicular mixed (C)	Follicle centre, follicular (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) Diffuse large cell (G)	Follicle centre, diffuse (small)
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; Ex. 1002 ¶ 30.

Skilled artisans recognized by August 1999 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 2; Ex. 1001, 2:50-66. Lymphomas categorized as intermediate- or high-grade were often studied together, as treatments were considered to be the same. Ex. 1002 ¶ 37; *see also, e.g.*, Ex. 1009, Shipp at 2 (studying diffuse mixed, DLCL, and immunoblastic large cell lymphomas together); Ex. 1006, Coiffier at 2-3 (studying four types of intermediate- and high-grade lymphomas); Ex. 1005, Link at 5 (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 ¶¶ 33-35.

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. As of August 1999, the standard-of-care chemotherapy for such patients required a combination of drugs, the most favored being CHOP. Ex. 1002 ¶¶ 34-35. As one prior art reference explained, as of June 1997, “CHOP, because of its low toxicity and ease of administration, . . . has been considered the standard of care for advanced stage diffuse large B cell lymphoma.” Ex. 1010, Martelli at 7.

The chemotherapy and radiation treatments work to target and kill the cancerous B-cells in the body. Ex. 1002 ¶ 33; Ex. 1011, Hiddemann II at 1-3. Although chemotherapy, especially CHOP, was the standard of care for patients suffering from intermediate- or high-grade NHL, chemotherapy was also understood to be less effective in certain patient populations. Ex. 1002 ¶ 39.

Specifically, a POSA would have understood that there are a number of risk or prognosis factors that reduced a patient's likelihood of recovery from DLCL. As explained by Martelli et al., "Current Guidelines for the Management of Aggressive Non-Hodgkin's Lymphoma" (June 1997) ("Martelli"), patients over 60 years of age and those with bulky disease are at higher risk of disease progression. Ex. 1010, 3. In addition to being correlated with the aggressiveness or grade of NHL, "prognosis deteriorates with advanced stage, increased tumor bulk (diameter > 10cm) and extranodal spread of nodal lymphoma." *Id.*; Ex. 1002 ¶ 39. Indeed, the greatest determinant of relative risk 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, Martelli at 2, Table I.

**B. Shipp taught that CHOP therapy was an effective treatment for patients with intermediate- and high-grade NHL accompanied by bulky disease.**

Although patients with bulky disease, defined in the claim as having at least one tumor  $> 10 \text{ cm}^2$ , could be particularly difficult to treat, Shipp et al., “High-Dose CHOP as Initial Therapy for Patients with Poor-Prognosis Aggressive Non-Hodgkin’s Lymphoma: A Dose-Finding Pilot Study” (Dec. 1995) (“Shipp”) taught that CHOP was the still standard of care for these patients because it has activity in bulky disease when used in appropriate concentrations. Ex. 1009, 1. As Shipp explained, skilled artisans had “attempted to improve the cure rate in aggressive NHL by optimizing the standard induction regimen that was administered to all patients.” *Id.* This was done “by adding new agents to [the] four-drug cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) backbone and/or by increasing the frequency of drug administration.” *Id.* In other words, the CHOP backbone therapy was the “standard induction regimen” administered to all aggressive NHL patients. *Id.*; Ex. 1002 ¶¶ 35-38, 48.

As Shipp further explained, however, “the subset of patients with bulky ( $\geq 10 \text{ cm}$ ) advanced-stage disease had only a 44% complete response (CR) rate and a 23%

---

<sup>2</sup> Ex. 1001, 8:41-47. Bulky disease patients can also have tumors smaller than 10 cm. *See, e.g.*, Ex. 1006, Coiffier at 3; Ex. 1002 ¶ 87.

5-year progression-free survival after treatment” with standard doses of non-CHOP chemotherapy regimens. Ex. 1009, 1. Shipp thus explored whether CHOP therapy, which “was as effective as other therapies” but also “had the most convincing dose-response relationships in aggressive NHL,” could be more effective in patients with bulky disease at higher doses without the toxicity of other chemotherapy drugs. *Id.*

Shipp—a reference that was not before the Examiner during prosecution of the ’244 patent—taught that patients with intermediate- and high-grade NHL (including patients with DLCL) accompanied by bulky disease respond to appropriate doses of CHOP therapy. Shipp studied 30 newly diagnosed patients with “diffuse mixed, diffuse large-cell, or large-cell immunoblastic lymphoma.” *Id.* at 2. That is, these patients all had intermediate- or high-grade NHL equivalent to categories “F,” “G,” and “H” of the working formulation, who also had “at least one area of tumor involvement  $\geq 10$  cm.” *Id.* at 2, 3 Table 1; Ex. 1002 ¶ 49.

The following chart summarizes the characteristics of the patients in the Shipp study:

Table 1. Characteristics of the Protocol Patients

Patient No.	Dose Level	Age (years)	Largest Mass Size (cm)	Stage*	PSt	LDH ( $\times$ normal)	AAI†
1	1	20	10.0	IV	1	2.0	HI
2	1	64	10.0	III	3	1.7	H
3	1	28	13.8	III	2	2.2	H
4	2	32	11.2	IV	0	1.8	HI
5	2	48	10.0	IV	0	1.7	HI
6	2	67	13.0	III	0	2.3	HI
7	2	39	10.0	III	0	2.1	HI
8	3	46	13.0	IV	1	1.5	HI
9	3	29	10.0	IV	1	1.4	HI
10	3	29	18.0	III	1	2.1	HI
11	3	61	10.0	III	0	0.9	U
13	3	23	10.0	IV	2	0.6	HI
14	3	60	10.0	III	0	2.4	HI
15	3	22	10.0	IV	1	1.0	U
16	3	33	20.0	III	0	2.0	HI
17	3	28	20.0	IV	3	1.2	H
18	3	49	12.0	IV	0	1.8	HI
19	3	38	15.0	IV	1	2.4	HI
20	3	40	15.0	III	0	1.1	HI
21	3	47	14.0	III	0	1.5	HI
22	3	50	15.0	III	1	1.4	HI
23	3	45	15.0	III	0	2.0	HI
24	3	22	13.0	IV	1	1.0	LI
25	3	48	20.0	IV	1	9.5	HI
26	3	44	14.0	IV	2	2.0	H
27	3	38	16.0	IV	0	1.3	HI
28	3	36	14.0	IV	0	0.8	LI
29	3	42	17.5	IV	1	1.3	HI
30	3	22	10.0	IV	1	0.6	LI
12§	4	58	12.0	IV	1	3.0	HI
Summary							
Median		39.5	13	IV 18 pts	0 13 pts	1.7	LI 5 pts
Range		20-67	10-20	III 12 pts	1 11 pts 2 3 pts 3 2 pts	0.6-9.5	HI 21 pts H 4 pts

Ex. 1009, 3, Table 1. Patients with a tumor less than 10 cm in diameter were excluded from the study. *Id.* at 2. The 30 patients (median age 39.5) had a median tumor size of 13 cm in diameter. Patients were divided into four different dosing regimens. *Id.* at 2, Fig. 1. Of note, the study included three patients > 60 years old, and one patient who was 60 years old. *Id.* at 3, Table 1. One of these elderly patients was assigned to the first dose level, another to the second, and two to the third dose level; the vast majority of all patients were assigned to the third dose level.

Shipp described the results of the patients in dose levels one, two, and four: “two of three patients at dose level one, two of four patients at dose level two, and the one patient at dose level four obtained [complete responses].” *Id.* at 5. The others in these dosage groups had at least a partial response. *Id.* at 6, Table 6. Of the 22 patients remaining, all of whom were in dose level three, 19 had a complete response (86%), two had a partial response (9%), and one had no response (4%). *Id.* at 5-6, Table 6.

Based on these data, Shipp concluded that “patients who are less likely to benefit from standard [i.e., CHOP] therapy may have a higher [complete response] rate with the high-dose CHOP regimen.” *Id.* at 7. Shipp’s data indicate that at least three of the four patients aged 60 or above responded to high-dose CHOP therapy. Ex. 1002 ¶¶ 50-51. As explained in the reference, one such patient was assigned to group one, one to group two, and two to group three. Ex. 1009, Shipp at 3, Table 1; Ex. 1002 ¶ 51. Within these groups, only one patient in group three had no response to therapy. Ex. 1009, Shipp at 6, Table 6; Ex. 1002 ¶ 51. This patient may or may not be one of the patients over 60. Thus, at least three of the four patients 60 years old or older with bulky disease had at least a partial, if not complete, response to the CHOP treatment. Ex. 1002 ¶¶ 50-51.

Shipp thus confirmed to a POSA that CHOP was the standard therapy for patients with intermediate-grade NHL, including DLCL, accompanied by bulky

disease. Ex. 1002 ¶¶ 51-54. It further taught that these patients, including such patients at least 60 years old, could be more effectively treated with higher doses of CHOP. *Id.*

**C. McNeil and other prior art taught that older patients were still at risk of toxicity from CHOP chemotherapy.**

Although CHOP was standard therapy for the treatment of bulky disease—and Shipp taught that even patients over 60 years old respond to higher doses of CHOP—the prior art taught that conventional or high doses of CHOP could lead to toxicity in older patients. Thus, there was a need in the art for improved therapy for such patients.

The McNeil reference—a news report from February 1998 in the *Journal of the National Cancer Institute*, which was also not before the Examiner during prosecution of the '244 patent—addressed this continuing search for improved therapies. McNeil reported a study that “confirms CHOP as the standard therapy for the elderly.” Ex. 1003, 2. Yet McNeil also explained that “treatment for intermediate-grade lymphoma—common among elderly NHL patients—is markedly less successful in older patients. CHOP cures only about half as many elderly patients as younger patients.” *Id.* at 1. In particular, patients over 60 years old had difficulty responding to the resulting toxicity from CHOP: “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.*; Ex. 1002 ¶ 59.

Due to this poorer tolerance for toxicity, patients over 60 could not withstand too many cycles of chemotherapy. “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].” Ex. 1003, McNeil at 1 (brackets in original). As confirmed by McNeil, skilled artisans thus recognized the need to find more successful treatments for the elderly: “We know from this prognostic index that we should be looking for an alternative for patients age 60 and above.” *Id.* (quoting Thomas Habermann, M.D.); *see also id.* at 1-2; Ex. 1002 ¶ 60.

Consistent with McNeil, Shipp itself reported that high toxicity was expected with its high-dosing regimens. In fact, “the protocol was expected to result in grade 4 hematologic toxicity,” Ex. 1009, 3, out of a toxicity scale of 1 to 5. Ex. 1002 ¶ 55. As Shipp explained: “The significant hematologic toxicity associated with the pilot induction regimen also underscores the need to administer this therapy with close monitoring and continued long-term follow-up.” Ex. 1009, 7. Thus, just as Shipp sought to find a high dose of CHOP that was less toxic than high doses of other chemotherapy drugs, a POSA would have been motivated to continue seeking more effective treatments that did not increase toxicity. Put simply, as McNeil reported, “[t]he search for other drug combinations that may be as effective but less toxic than CHOP continues.” Ex. 1003, 2.

- D. McNeil suggested, and Link confirmed, that the combination of rituximab and CHOP was likely more effective, but no more toxic, than CHOP alone for DLCL patients—including patients above 60 years old.**

One such drug combination therapy had emerged a few years before August 1999: the combination of CHOP and the monoclonal antibody rituximab. Monoclonal antibodies are proteins or protein chains designed to bind themselves to a specific antigen. Ex. 1004, Rituxan™ label at 1. They can be “chimeric”—i.e., biologically engineered antibodies that comprise human and mouse antibody components. Ex. 1002 ¶ 41. 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 ¶¶ 41-42. 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 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, thus enabling the B-cells’ destruction. Ex. 1002 ¶ 42. As explained by 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. 1004, 1. The label explains 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 on >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. The FDA approved label did not report on studies of rituximab’s efficacy in higher 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 stem cell transplantation. Ex. 1022, 11. The median age of the patient population was 59 and included patients as old as 62. *Id.* 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 [stem cell transplantation].” *Id.*

Tsai was hardly alone in experimenting with or suggesting rituximab for off-label treatments. McNeil addressed this new therapy and specifically suggested combining rituximab with CHOP in patients over 60 with intermediate-grade NHL:

“One alternative [for NHL patients aged 60 and above] could be CHOP plus the monoclonal antibody [rituximab].” Ex. 1003, 1; Ex. 1002 ¶ 60.

By March 1998, still more than a year and a half before the date of the claimed invention, a study of the combination of CHOP and 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.

In this study of 31 patients (median age 49), Link reported administration of “rituximab 375 mg/m<sup>2</sup> 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 class “G” diffuse large B-cell NHL. *Id.* Of the 30 patients evaluable for response, all but one responded. *Id.*; Ex. 1002 ¶ 63. Specifically, 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. Therefore, Link specifically taught that the combination of CHOP and rituximab successfully treated patients with diffuse large B-cell lymphoma.

Critically, Link 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 ¶ 64. 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 ¶ 64. Indeed, the Examiner explained 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, 4; *see also* Ex. 1002 ¶ 65.

**E. Coiffier confirmed that rituximab is effective with minimal toxicity in elderly patients with intermediate grades of NHL and in bulky disease.**

The Coiffier reference, published before the priority date in September 1998 in the journal *Blood*, studied rituximab in elderly patients and concluded it was likely to be effective and non-toxic in this patient population. Coiffier studied two different dose levels of rituximab in patients with intermediate- and high-grades of NHL. Ex. 1006, 1. Sixty-one (61) percent of the patients in the first dose level had DLCL and 50 percent of the patients in the second dose level had DLCL. *Id.* at 2, Table 1. The median age of both treatment groups was over 60—62.5 in one level and 65 in the other. *Id.* Thirty-seven (37) percent of the patients with DLCL responded. *Id.* at 3, Table 3.

Coiffier thus showed that rituximab was safe and efficacious in elderly patients with DLCL. Ex. 1002 ¶ 66. Coiffier concluded by encouraging further testing of rituximab in combination with chemotherapy: “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 (emphasis added).

Coiffier also taught that rituximab had significant activity in patients with bulky disease. As discussed, the patent defines bulky disease as “at least 1 tumor > 10 cm in diameter,” Ex. 1001, 8:46-47, but patients with bulky disease commonly have more than one tumor, including tumors < 10 cm in diameter. Ex. 1002 ¶ 87. Coiffier teaches that rituximab monotherapy treats patients with bulky disease, at least with regard to the patients’ smaller tumors—with 46 percent of patients responding if they had tumors <5 cm, and 21 percent responding if they had tumors between 5 and 10 cm. Ex. 1006, 3, Table 3.

## **VI. THE ’244 PATENT CLAIMS, SPECIFICATION, AND PROSECUTION HISTORY**

The ’244 patent claims the following:

1. A method of treating a patient with diffuse large cell lymphoma, comprising administering an unlabeled chimeric anti-CD20 antibody and CHOP (cyclophosphamide, hydroxycarbonyl doxorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient,

wherein the patient is >60 years old and has bulky disease (tumor > 10 cm in diameter).

2. The method of claim 1 wherein the chimeric antibody is rituximab.

#### **A. The Patent Specification**

According to the patent specification, patients with intermediate-grade lymphomas survive only about 2-5 years. Ex. 1001, 1:20-28. The specification explains: “Intermediate- and high-grade lymphomas are much more aggressive at the time of diagnosis than are low-grade lymphomas, where patients may survive an average of 5-7 years with conventional therapies. Intermediate- and high-grade lymphomas are often characterized by large extranodal bulky tumors and a large number of circulating cancer cells, which often infiltrate the bone marrow of the patient.” Ex. 1001, 1:29-35. The specification goes on to say that “[c]onventional therapies have included chemotherapy and radiation, possibly accompanied by either autologous or allogeneic bone marrow or stem cell transplantation if a suitable donor 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, 1:36-43. Although rituximab was already approved for low grades of NHL, the inventors claim to have discovered that rituximab “may be effective to treat more aggressive lymphomas as well.” Ex. 1001, 2:6-13.

**B. Prosecution History**

The '244 patent was filed on July 28, 2000, under U.S. Application No. 09/628,187. As originally filed, claims 1-16 were directed to a method for treating or alleviating the symptoms of intermediate- or high-grade NHL accompanied by bulky disease (without specifying a minimum diameter) using a therapeutically effective amount of rituximab and CHOP. After a series of rejections and amendments over the course of several years, the applicants finally arrived at the allowable claim language. And while this Petition addresses prior art references the Examiner did not consider during prosecution, the Examiner's final rejection is illustrative of the prior art considerations and rejections the Examiner made before the claims were allowed and are therefore relevant to this Petition.

On June 26, 2012, the Examiner rejected the claims of the application that the Examiner ultimately issued as the '244 patent as obvious over articles published by Link et al. (Ex. 1005), Davis et al. (Ex. 1007), and Coiffier et al. (Ex. 1006). The Examiner concluded that "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Link, comprising the combination of anti-CD20 (rituximab) therapy with CHOP therapy for the treatment of non-Hodgkin's [lymphoma], to treat patients with diffuse large cell lymphoma, bulky disease and at an age greater than 60 years old, because Davis teaches that rituximab is effective in patients with lymphoma and

bulky disease, and because Coiffier teaches that rituximab has low toxicity and significant clinical activity.” Ex. 1019, 4. The Examiner found that because a POSA would have been motivated to use the methods taught in the three above-mentioned references, the invention would be obvious and thus the claims were rejected.

In an attempt to distinguish the cited art, the applicants primarily focused on the treatment response rates of category “G” lymphoma (DLCL) patients with bulky disease. The applicants responded to the rejection by first pointing out that “diffuse large cell lymphoma recited in claims 102 and 103 is an intermediate-grade lymphoma, identified as *grade ‘G’* in the IWF Classification system.” Ex. 1020, 4 (emphasis in original). The applicants then pointed out that Link does not “separately discuss” patients with grade “G” lymphomas. *Id.* at 4-5. Next, they critiqued Davis as not entirely applicable because it only “conclude[s] that rituximab is safe and effective in patients with bulky [low-grade or follicular] NHL, i.e., with grade ‘A,’ ‘B,’ ‘C,’ and ‘D’ lymphomas.” *Id.* at 5.

Lastly, the applicants argued that Coiffier did not render the invention obvious, but in fact taught away from the claimed invention. Because “none of the [five] patients who had tumor lesions  $\geq 10$  cm in size responded to treatment with rituximab,” they argued that Coiffier “does not create a reasonable expectation that a combination treatment with an anti-CD20 antibody, such as rituximab, and CHOP would be effective in treating patients with diffuse large cell lymphoma of  $\geq [10$  cm]

in size (bulky disease).” *Id.* at 6. Instead, they argued, Coiffier “actually teaching [*sic*] away from the treatment method claimed in the present application.” *Id.*

In response to these arguments, the Examiner allowed the claims of what became the ’244 patent. Ex. 1021, 4. The Examiner withdrew the rejections, agreeing with applicants “that Coiffier provides teachings away from the claimed invention.” *Id.* As the Examiner noted, Coiffier “teaches that none of the patients with tumor lesions over 10 cm in size responded to treatment with rituximab (Table 3, page 1929).” *Id.* As a result, according to the Examiner, a POSA “would not be motivated to combine the teachings of Link and Davis and Coiffier to arrive at the claimed method.” *Id.*

As discussed in Parts IX.A-IX.B, the Examiner was correct when she initially found the claims obvious. The Examiner, however, then incorrectly viewed Coiffier as teaching away from the claimed invention—a finding made without the benefit of the Shipp reference discussed above, which was not disclosed by the applicant.

## **VII. CLAIM CONSTRUCTION**

### **A. Plain and Ordinary Meaning**

The terms of the ’244 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).

### **VIII. PRIOR ART STATUS OF CITED REFERENCES**

As shown below and in the Declaration of Petitioner’s expert librarian, Dr. Scott Bennett (Ex. 1016), each of the four references that Petitioner relies upon for the grounds of unpatentability asserted in this Petition—*i.e.*, Shipp (Ex. 1009); McNeil (Ex. 1003); Link (Ex. 1005); and Coiffier (Ex. 1006)—and 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 ’244 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. Shipp (Ex. 1009)**

First, as Dr. Bennett shows, Shipp is an authentic copy of a research paper by Margaret Shipp published in the December 1995 issue of the *Journal of Clinical*

*Oncology*. Ex. 1016 ¶¶ 37–41. Public records confirm that the *Journal* is a periodical that was first published in 1983 and is held by 778 libraries worldwide. *Id.* ¶ 42. 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 December 1995 issue of the *Journal of Clinical Oncology*, which contains Shipp, was processed by that library on December 11, 1995. *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 December 11, 1995. *Id.* Therefore, Shipp was available to the public before August 11, 1998. *Id.* ¶¶ 44-46. Thus, Shipp is prior art to the '244 patent as a publicly accessible printed publication under 35 U.S.C. § 102(b).

**B. McNeil (Ex. 1003)**

Second, 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 ¶¶ 47-51. Public records confirm that the *Journal* is a periodical that was first published in 1940 and is held by 1,302 libraries worldwide. *Id.* ¶ 52.

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.* ¶ 53. 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.* ¶¶ 54-55.

Accordingly, McNeil is prior art to the '244 patent as a publicly accessible printed publication under 35 U.S.C. § 102(b).

**C. Link (Ex. 1005)**

Third, 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 ¶¶ 56-61. 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.* ¶ 63. The attendees of the meeting included numerous oncologists with experience treating NHL patients. Ex. 1002 ¶ 62. 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 abstract, 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 ¶ 64; *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 ¶ 65. 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.* ¶¶ 66-67. 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.* ¶ 66 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 '244 patent as a publicly accessible printed publication under 35 U.S.C. § 102(b).

#### **D. Coiffier (Ex. 1006)**

Fourth, Coiffier is an authentic copy of a news report by B. Coiffier published in the September 15, 1998 issue of *Blood*. Ex. 1016 ¶¶ 68-73. Public records confirm that *Blood* is a periodical that was first published in 1946 and is held by 965 libraries worldwide. *Id.* ¶ 74. *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.* ¶ 75. 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 by early October 1998. *Id.* ¶¶ 76-78.

Accordingly, Coiffier is prior art to the '244 patent as a publicly accessible printed publication under 35 U.S.C. § 102(a).

**E. Rituxan™ label (Ex. 1004)**

Lastly, 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 ¶¶ 79-83. 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.* ¶ 81.<sup>3</sup>

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.* 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.* ¶ 81; *see also, e.g., IBM Corp. v. Intellectual Ventures II LLC*, No. IPR2015-00089, Paper 44 at 57 (PTAB Apr. 25, 2016) (relying on

---

<sup>3</sup> 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 ¶ 82. 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.* ¶¶ 82-83.

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 ’244 patent as a publicly accessible printed publication under 35 U.S.C. § 102(b).

## **IX. ANALYSIS OF GROUNDS FOR TRIAL**

The ’244 patent would have been obvious to a person of ordinary skill in the art at the time of the claimed invention. The standard practice for treating cancer patients with DLCL accompanied by bulky disease was to use chemotherapy, of

which CHOP was the preferred regimen. Ex 1009, Shipp at 1. However, patients over 60 needed a more effective treatment without additional toxicity. Ex 1003, McNeil at 1. Thus, “the general problem that confronted the inventor before the invention was made,” *see In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2011), was whether new therapies would have improved the effectiveness of existing treatments without increasing toxicity. Ex. 1002 ¶¶ 56-60; *see also* Ex. 1003, McNeil at 1.

In light of that problem, a POSA would have been motivated to add rituximab to a regimen of CHOP for patients over 60 with bulky disease, particularly in light of Shipp’s teaching that CHOP treats patients over 60 years old with bulky disease and Link’s teaching that the addition of rituximab adds efficacy but not toxicity. Ex. 1005, 5. McNeil expressly suggested combining these teachings by suggesting “CHOP plus the monoclonal antibody [rituximab]” as an “alternative” for patients over 60 years old with intermediate-grade NHL. Ex. 1003, 1.

These references thus gave a POSA a “finite number of identified, predictable solutions” to a known problem in the art—the problem of improving efficacy in DLCL patients over 60 with bulky disease, without increasing toxicity. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). The prior art motivated a skilled artisan to treat such patients with the claimed combination of CHOP with an anti-CD20 antibody—in particular, with rituximab, which was the *only* known anti-CD20 antibody in the art at the time of the claimed invention. Given the state of the art at

that time, a skilled artisan also would have reasonably expected success in pursuing this combination therapy. *See In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988); Ex. 1002 ¶¶ 74-75.

**A. Ground 1: Claims 1-2 would have been obvious over Shipp and Link in view of McNeil.**

**1. Claim 1 would have been obvious.**

Claim 1 of the '244 patent recites “[a] method of treating a patient with diffuse large cell lymphoma, comprising administering an unlabeled chimeric anti-CD20 antibody and CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient, wherein the patient is > 60 years old and has bulky disease (tumor > 10 cm in diameter).” This claim, which contains no dosing limitations, would have been obvious to a POSA over Shipp and Link in view of McNeil.

- a. “A method of treating a patient with diffuse large cell lymphoma comprising administering . . . CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient, wherein the patient . . . has bulky disease (tumor > 10 cm in diameter).”**

The '244 patent's specification explains under “background of the invention” that chemotherapy was a “conventional” therapy for intermediate-grade lymphomas, including those accompanied by bulky disease:

Intermediate- and high-grade lymphomas are much more aggressive at the time of diagnosis than are low-grade lymphomas,

where patients may survive an average of 5-7 years with conventional therapies. Intermediate- and high-grade lymphomas are often characterized by large *extranodal bulky tumors* and a large number of circulating cancer cells, which often infiltrate the bone marrow of the patient.”

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 donor 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, 1:29-42 (emphasis added). Thus, traditional chemotherapy such as CHOP was a “conventional therapy,” i.e., a part of the prior art, for “[i]ntermediate- and high-grade lymphomas . . . often characterized by large extranodal bulky tumors.” *Id.* at 1:33-34. The specification later states that “diffuse large cell lymphoma” is an intermediate-grade lymphoma. *Id.* at 2:42-45.

These statements are concessions that chemotherapy was already used in the prior art to treat patients with DLCL accompanied with bulky disease. “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”).

Putting aside these concessions by the applicants, the prior art itself disclosed the use of CHOP chemotherapy to DLCL patients with bulky disease. Ex. 1002 ¶¶ 76-81. Shipp—which, again, was not before the Examiner—studied the effect of CHOP on patients with “diffuse mixed, diffuse large-cell, or large-cell immunoblastic lymphoma” who had bulky disease  $\geq 10$  cm. Ex. 1009, 2. Shipp taught that CHOP therapy “was as effective as other therapies” but also “had the most convincing dose-response relationships in aggressive NHL,” and thus could be more effective in patients with bulky disease at higher doses without the toxicity of other chemotherapy drugs. *Id.* at 1. That was indeed the result. Almost all patients with tumors  $\geq 10$  cm in diameter had complete or partial responses to the prescribed CHOP therapy. *Id.* at 6, Table 6. Shipp concluded that “patients who are less likely to benefit from standard therapy may have a higher [complete response] rate with the high-dose CHOP regimen.” *Id.* at 7.

**b. “wherein the patient is > 60 years old”**

Shipp also taught that CHOP therapy could be used to treat patients over 60 years old with intermediate grades of lymphoma, such as DLCL, who also had bulky disease. Ex. 1002 ¶¶ 51-52. Four patients studied in Shipp were at least 60 years

old with bulky disease  $\geq 10$  cm, and at least three of them responded to its high-dose CHOP therapy. Ex. 1009, 6, Table 6; *see also* Ex. 1002 ¶ 51.

McNeil—also not considered by the Examiner—confirmed that CHOP therapy was the standard treatment for patients over 60. This reference suggested that “CHOP plus the monoclonal antibody” rituximab could be “an alternative” therapy to CHOP alone, reporting on a “new trial” “for patients age 60 and over” who will “receive either CHOP alone or CHOP with Rituxan, which targets the B-cell protein CD20.” Ex. 1003, 1.

**c. “comprising administering an unlabeled chimeric anti-CD20 antibody and”**

As discussed, Shipp disclosed that CHOP therapy was the standard of care for DLCL patients with bulky disease, and even for patients over 60 years old with intermediate-grade lymphomas such as DLCL accompanied by bulky disease. Ex. 1002 ¶¶ 48-55. Shipp thus taught “[a] method of treating a patient with diffuse large cell lymphoma, comprising administering . . . CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient, wherein the patient is  $> 60$  years old and has bulky disease (tumor  $> 10$  cm in diameter).” Ex. 1001, 8:41-47; Ex. 1009, 6; Ex. 1003, McNeil at 1.

Shipp taught that although patients with DLCL and bulky disease were successfully treated by CHOP, “the protocol was expected to result in grade 4

hematologic toxicity.” Ex. 1009, 3. As Dr. Ozer explained, this was on a scale of 1 to 5, suggesting a high level of toxicity (which was to be expected). Ex. 1002 ¶ 55.

A POSA would have been familiar with this background—i.e., with the general trade-off in chemotherapy between efficacy and toxicity. Ex. 1002 ¶¶ 56-57. A POSA would have further known that elderly patients were particularly susceptible to the toxicity of chemotherapy, and that bulky disease > 10 cm might sometimes require high doses of CHOP. Ex. 1002 ¶¶ 56-60. There thus existed a need in the art for treatments that improved efficacy without additional toxicity. *Id.*

In light of this background, Link would have motivated a POSA to add the “chimeric anti-CD20 antibody” rituximab—the only FDA-approved chimeric anti-CD20 antibody—to the therapy taught by Shipp. Ex. 1001, 8:41-47. Link studied the combination of CHOP and rituximab, which it described as a “chimeric murine/human monoclonal antibody that targets the CD20 antigen,” Ex. 1005, 5, in 21 patients with DLCL, among other patients. All but one patient in the study responded, thus specifically teaching that the combination of CHOP and rituximab successfully treated patients with DLCL. *Id.*

Critically, the Link study further 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 ¶ 64. Link taught “[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 therapy alone and may offer *higher response rates*.” Ex. 1005, 5 (emphases added). In other words, CHOP combined with rituximab was reasonably expected to offer more efficacy without additional toxicity. Ex. 1002 ¶¶ 64-65.

Thus, as discussed further below, the very problem confronting a POSA in this field—the need for more efficacy without additional toxicity—would have motivated the POSA to combine the teachings of Link and Shipp for the treatment of patients over 60 with DLCL accompanied by bulky disease. Ex. 1002 ¶¶ 61-65.

#### **d. Motivation to combine**

McNeil confirmed the motivation for a POSA to combine the teachings of Shipp and Link. McNeil explained the problem elderly patients experienced with CHOP therapy—the standard treatment for DLCL. Although CHOP was effective, older patients had “poorer outcomes” because “CHOP, like some other chemotherapy regimens, is more toxic in this age group.” Ex. 1003, McNeil at 1. McNeil thus elaborated 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].” *Id.* (brackets in original). McNeil emphasized that there was therefore a need in the art for treatments that improved efficacy without increasing toxicity: “We know from this prognostic index that we *should be looking*

*for an alternative for patients age 60 and above.”* *Id.* (emphasis added). As McNeil put it: “[T]he search for other drug combinations that may be as effective but less toxic than CHOP continues.” *Id.* at 2.

McNeil would have motivated a POSA to combine the teaching of Link with the teaching of Shipp, because adding rituximab could result in increased efficacy without additional toxicity. That is, a POSA would recognize that rituximab could replace some of the CHOP doses in elderly patients and thus reduce toxicity, or simply increase the efficacy of existing CHOP regimens without any added toxicity. Ex. 1002 ¶¶ 56-58. As McNeil explained: “We know . . . that we should be looking for an alternative [NHL therapy] for patients age 60 and above,” and “[o]ne alternative could be CHOP plus the monoclonal antibody [rituximab].” Ex. 1003, 1.

The claimed combination of CHOP and rituximab thus would have been obvious to a POSA in view of Shipp, Link, and McNeil. Where a prior art reference—such as McNeil—suggests a combination, that is a “clear motivation to combine.” *See Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1289-90, 1293 (Fed. Cir. 2013) (where a prior art reference recommended combining two drugs into a single formulation to improve patient compliance, prior art supplied a “clear motivation to combine”).

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 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 and 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 and rituximab.

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 the skilled artisan would have had a reasonable expectation of success from doing so.” *In re*

*Cyclophosphamide Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012) (citations omitted); *see also* Ex. 1002 ¶¶ 80-81.

**2. Claim 2 would have been obvious.**

Claim 2 is also obvious. Claim 2 recites “[t]he method of claim 1, wherein the chimeric antibody is rituximab.” Ex. 1001, 8:48-49. As explained above, this claim is obvious over Shipp, McNeil, and Link—the latter two of which expressly taught the combined use of CHOP and rituximab (a chimeric anti-CD20 antibody). Ex. 1009, Shipp at 6, Table 6; Ex. 1003, McNeil at 1; Ex. 1005, Link at 5; Ex. 1002 ¶¶ 61-65, 82.

**B. Ground 2: Claims 1-2 would have been obvious over Shipp and Coiffier**

Alternatively, claims 1-2 would have been obvious over Shipp and Coiffier.

**1. Claim 1 would have been obvious.**

- a. “A method of treating a patient with diffuse large cell lymphoma comprising administering . . . CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy to the patient, wherein the patient is > 60 years old and has bulky disease (tumor > 10 cm in diameter).”**

As explained, Shipp taught all of the elements of claim 1 with the exception of using a monoclonal antibody like rituximab in combination with CHOP therapy. That is, Shipp taught that CHOP was the standard therapy for DLCL patients with bulky disease, and even more specifically for intermediate-grade bulky disease patients over 60 years old. Ex. 1009, 6, Table 6; Ex. 1002 ¶¶ 51-52, 83.

**b. “comprising administering an unlabeled chimeric anti-CD20 antibody and”**

A POSA would have been motivated to combine rituximab, a “chimeric anti-CD20 antibody,” to the regimen disclosed by Shipp in light of Coiffier. Coiffier taught that rituximab—a chimeric anti-CD20 antibody—had activity in intermediate grades of NHL, but without the toxicity of normal CHOP regimens. Ex. 1006, 5-6. Coiffier demonstrated that although one of the “dominant features of [its patient] population [was] a relatively old age,” the response rate was “above the minimal desirable threshold that was defined by the protocol and is similar to what would be expected with single-agent therapy in this patient population.” *Id.* at 5. A POSA would have understood from Coiffier that rituximab had anti-cancerous activity in elderly patients with NHL and was a viable treatment option for them. Ex. 1002 ¶¶ 66-69.

Coiffier also taught that rituximab had minimal toxicity, thus suggesting it would be particularly useful in elderly patients susceptible to toxicity with CHOP. Ex. 1002 ¶¶ 68-69. “Importantly,” the authors wrote, “these results were obtained without the characteristic toxicity of combination chemotherapy regimens and over a shorter treatment period.” Ex. 1006, Coiffier at 6. Coiffier explicitly suggested that rituximab be combined with chemotherapy: “Rituximab has significant activity in DLCL and MCL patients and *should be tested in combination with chemotherapy in such patients.*” *Id.* at 1 (emphasis added). A POSA thus would have been

motivated to add the anti-CD20 antibody rituximab to the CHOP chemotherapy of Shipp. That is, a POSA either could have added rituximab to fewer cycles of CHOP to achieve the same efficacy as CHOP monotherapy but with less toxicity, or added rituximab to the normal number of CHOP cycles for more efficacy but no additional toxicity. Ex. 1002 ¶¶ 66-69, 85.

**c. There was no teaching away.**

During prosecution, the applicants persuaded the Examiner to allow the claims of what is now the '244 patent on the basis that Coiffier purportedly taught away from the claimed invention. Ex. 1020, 5-6; Ex. 1021, 4. Specifically, the applicants asserted that Coiffier “does not create a reasonable expectation that a combination treatment with an anti-CD20 antibody, such as rituximab and CHOP would be effective in treating patients with diffuse large cell lymphoma of  $\geq$  [10 cm] in size (bulky disease).” Ex. 1020 at 6. Instead, the applicants argued, “it actually teaching [*sic*] away from the method of treatment claimed in the patent.” *Id.*

The Examiner incorrectly found that Coiffier taught away from the claimed invention. According to the Examiner, the five patients with bulky disease ( $\geq$  10 cm) in the Coiffier study did not “respond” to rituximab *monotherapy* therapy in that study. Ex. 1006, 3, Table 3. But Coiffier does not teach away from the claimed invention, which is directed to *combination therapy* that includes both CHOP and rituximab.

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) (citation omitted). The applicants did not apply this standard. Instead, they summarily and incorrectly argued that there is no “reasonable expectation that a combination treatment” with CHOP and rituximab “would be effective in treating patients with diffuse large cell lymphoma of  $\geq$  [10 cm] in size (bulky disease).” Ex. 1020, 6. But a POSA reading Coiffier along with Shipp would have had such a reasonable expectation. Indeed, Coiffier actually would have *encouraged* a POSA to add rituximab to CHOP regimens for the treatment of bulky disease, for two reasons. *See* Ex. 1002 ¶¶ 83-85, 88-89.

First, a POSA would have been motivated to combine rituximab with CHOP precisely because Coiffier taught that rituximab *monotherapy*—i.e., without other drugs—was insufficient to treat tumors  $\geq$  10 cm in diameter. As discussed, Coiffier taught a POSA that rituximab can treat bulky tumors smaller than 10 cm in diameter. Ex. 1002 ¶¶ 86-87; Ex. 1006, 3, Table 3. In particular, Coiffier showed a 21% response in patients with lesions between 5 and 10 cm, and a 46% response—greater than the conventional 44% response reported in Shipp for tumors  $>$  10 cm—in patients with lesions less than 5 cm. Ex. 1006, 3, Table 3. Thus, a POSA looking to treat patients with bulky tumors larger than 10 cm in diameter would not have

given up on rituximab. Instead, a POSA would have been motivated to investigate combination therapy with rituximab—especially combination with another drug (or drugs) that would reduce the size of such large tumors such that they could be effectively treated with rituximab, as taught by Coiffier. Ex. 1002 ¶¶ 86-88. That, indeed, was the teaching of Coiffier itself: “Rituximab has significant activity in DLCL and MCL patients and *should be tested in combination with chemotherapy* in such patients.” Ex. 1006, 1 (emphasis added).

Shipp would have motivated a POSA to combine rituximab with CHOP, because Shipp taught that CHOP therapy can reduce tumor size by at least 50 percent—explaining that a partial response “was defined as greater than 50% reduction in the largest dimension of each site of measurable disease for at least 1 month.” Ex. 1009, 3. Indeed, in Shipp, *all but one patient* achieved at least this partial response. *Id.* at 6, Table 6. Thus, these patients all experienced reductions in their tumor sizes to sizes that, according to Coiffier, were treatable by rituximab. Coiffier would have motivated a POSA to combine rituximab to the therapy discussed in Shipp, thus leading directly to the claimed invention—the opposite of teaching away. Ex. 1002 ¶¶ 86-89.

Second, a POSA would have been independently motivated by Coiffier to combine CHOP with rituximab to treat patients with bulky disease. While patients with bulky disease have *at least one* tumor  $\geq 10$  cm in size, they frequently have

additional tumors of varying sizes. Ex. 1002 ¶¶ 87-88. Again, Coiffier confirmed that these tumors *did respond* to rituximab. Ex. 1006 at 3, Table 3. Thus, at the very least, a POSA would have been motivated to combine CHOP with rituximab to improve therapy as to those smaller tumors in patients with bulky disease.

Most importantly, Coiffier never criticizes, discredits, or otherwise discourages—expressly or implicitly—using rituximab with CHOP. Therefore, as explained in the declaration of Dr. Ozer, Coiffier teaches toward, not away, from the claimed invention. That is, a skilled artisan would have been motivated to combine Shipp and Coiffier knowing that CHOP therapy would reduce tumor size and that rituximab could treat the smaller tumors effectively. Ex. 1002 ¶¶ 86-89.

**2. Claim 2 would have been obvious.**

Claim 2 also would have been obvious. Claim 2 recites “[t]he method of claim 1, wherein the chimeric antibody is rituximab.” Ex. 1001, 8:48-49. This claim is obvious over Shipp and Coiffier for the reasons stated above, and because Coiffier specifically showed the effectiveness of rituximab in elderly patients and in bulky disease. Ex. 1009, Shipp at 6, Table 6; Ex. 1006, Coiffier at 3, Table 3. Thus, for the same reasons claim 1 is obvious, claim 2 is also obvious. Ex. 1002 ¶¶ 82-89.

**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. Ex. 1002 ¶ 22, 73.

Regardless, 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”—a showing made above. *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).

## **X. CONCLUSION**

For the foregoing reasons, the Board should institute *inter partes* review and cancel claims 1-2 of the '244 patent as unpatentable.

Dated: April 27, 2017

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

Respectfully submitted,

/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 11,086 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 27, 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 27, 2017, true and correct copies of the foregoing PETITION FOR *INTER PARTES* REVIEW, and all Exhibits thereto, were served by overnight courier service on the Patent Owner at the correspondence address of record for U.S. Patent No. 8,557,244 B1, 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 27, 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*