Trials@uspto.gov
571-272-7822

Paper No. 10
Entered: October 23, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

BIOGEN, INC.,
Patent Owner.

Case IPR2017-01229
Patent 8,206,711 B2

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

HARLOW, *Administrative Patent Judge.*

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Celltrion, Inc. ("Petitioner"), filed a Petition requesting an *inter partes* review of claims 1–9 of U.S. Patent No. 8,206,711 B2 (Ex. 1001, "the '711 patent"). Paper 3 ("Pet."). Biogen, Inc. ("Patent Owner") filed a Preliminary Response. Paper 8 ("Prelim. Resp."). We have authority to determine whether to institute an *inter partes* review under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." *See also* 37 C.F.R. § 42.4 (a). For the reasons set forth below, we deny the Petition.

A. Related Matters

The parties inform us of no related pending litigations. Pet. 4; Paper 4, 2. In addition to the instant proceeding, Petitioner has filed two petitions for *inter partes* review of related U.S. Patent No. 7,682,612 B1 (IPR2017-01227 and IPR2017-01230). Pet. 4; Paper 4, 2.

B. The '711 Patent

The '711 patent is titled "Treatment of Chronic Lymphocytic Leukemia Using Anti-CD20 Antibodies." Ex. 1001, [54]. The '711 patent discloses therapeutic regimens involving the administration of anti-CD20 antibodies for the treatment of chronic lymphocytic leukemia ("CLL"). *Id.* at Abstract, 2:16–21. "[A] particularly preferred chimeric anti-CD20

antibody is RITUXAN® (rituximab), which is a chimeric gamma 1 anti-human CD20 antibody." *Id.* at 3:18–20.

With regard to dosing, the '711 patent discloses that "[t]ypically effective dosages will range from about 0.001 to about 30 mg/kg body weight, more preferably from about 0.01 to 25 mg/kg body weight, and most preferably from about 0.1 to about 20 mg/kg body weight." *Id.* at 3:50–54. "Such administration may be effected by various protocols, e.g., weekly, bi-weekly, or monthly, dependent on the dosage administered and patient response." *Id.* at 3:55–57. In Example 3, the '711 patent reports clinical trial results in which patients were treated with varying doses of rituximab, including a study of CLL patients treated with one dose of 375 mg/m^2, and three subsequent weekly doses of 500–1500 mg/m^2. *Id.* at 6:8–30.

C. Illustrative Claims

Independent claims 1 and 9, reproduced below, are illustrative of the challenged claims of the '711 patent.

> 1. A method of treating chronic lymphocytic leukemia (CLL) in a human patient, comprising administering rituximab to the patient in an amount effective to treat the CLL, wherein the rituximab is administered to the patient at a dosage of 500 mg/m^2.

Ex. 1001, 8:17–21.

> 9. A method of treating chronic lymphocytic leukemia (CLL) in a human patient, comprising administering rituximab to the patient in an amount effective to treat the CLL, wherein the rituximab is administered to the patient at dosages of 500 mg/m^2, and further comprising administering a chemotherapeutic regimen to the patient, wherein the

> chemotherapeutic regimen comprises fludarabine and cyclophosphamide.

Id. at 8:36–43.

The challenged dependent claims variously add to claim 1 requirements concerning the administration of chemotherapeutic regimens, the frequency of rituximab administration, and the use of radiolabeled anti-CD20 antibody. *Id.* at 8:22–35.

D. Evidence Relied Upon

Petitioner relies upon the following prior art references (Pet. 26–31):

Batata, A. & Shen, B., *Relationship between Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: A Comparative Study of Membrane Phenotypes in 270 Cases*, 70(3) CANCER 625–632 (1992) (Ex. 1008) ("Batata").

Maloney, D.G. et al., *Phase I Clinical Trial Using Escalating Single-Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients with Recurrent B-Cell Lymphoma*, 84(8) BLOOD 2457–2466 (1994) ("Ex. 1009) ("Maloney 1994").

Kipps, T.J., Chapter 106: Chronic lymphocytic leukemia and related diseases, *Williams Hematology*, 1017–1039 (E. Beutler, et al., eds., 5th ed. 1995) (Ex. 1055) ("Kipps").

Public Hearing Transcript, Biological Response Modifiers Advisory Committee, Center for Biological Evaluation and Research, Food and Drug Administration, nineteenth meeting (July 25, 1997) (Ex. 1007) ("FDA Transcript").

Archived website for Leukemia Insights Newsletter, 3(2) (Archived on February 2, 1999) (Ex. 1006) ("MD Anderson Newsletter").[1]

Byrd, J.C. et al., *Old and New Therapies in Chronic Lymphocytic Leukemia: Now Is the Time for a Reassessment of Therapeutic Goals*, 25(1) SEMIN. ONCOL. 65–74 (1998) (Ex. 1010) ("Byrd").

M. Keating et al., *Early Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab As Initial Therapy for Chronic Lymphocytic Leukemia*, 23(18) J. CLIN. ONCOL. 4079–4088 (2005) (Ex. 1064) ("Keating").

Petitioner also relies upon the Declaration of Michael Andreeff, M.D. (Ex. 1005) to support its contentions.

E. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 6):

Claim(s)	Basis	Reference(s)
1, 5, 8	§ 102	MD Anderson Newsletter
7, 9	§ 102	Keating
6	§ 103	Keating and MD Anderson Newsletter
2–4, 9	§ 103	MD Anderson Newsletter and Byrd
6, 7	§ 103	MD Anderson Newsletter, Byrd, and Kipps
1, 5–8	§ 103	FDA Transcript, Batata, and Maloney

[1] Petitioner contends that MD Anderson Newsletter was also available as a print version (Ex. 1061).

II. ANALYSIS

A. Claim Construction

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

Petitioner and Patent Owner propose constructions for certain claim terms. Pet. 23–25; Prelim. Resp. 18–28. In view of our analysis, we determine that construction of claim terms is not necessary for purpose of this Decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (Only terms which are in controversy need to be construed, and only to the extent necessary to resolve the controversy).

B. Priority Date of the '711 Patent

The '711 patent issued from U.S. Patent Application No. 12/629,472 ("the '472 application"), filed on December 2, 2009. Ex. 1001, [21], [22]. The '711 patent is a continuation of U.S. Patent Application No. 09/436,347 ("the '347 application"), filed November 9, 1999, now U.S. Patent No. 7,682,612. *Id.* at [63]. The '711 patent claims priority to U.S. Provisional Patent Application No. 60/107,658 ("the '658 provisional application"), filed November 9, 1998. *Id*. at [60].

Petitioner argues that claims 2–4 of the '711 patent are entitled to a priority date of no earlier than November 9, 1999. Pet. 21. Petitioner likewise asserts that claims 6, 7, and 9 of the '711 patent are entitled to a priority date of no earlier than December 2, 2009. *Id*. at 21, 23.

"Patent claims are awarded priority on a claim-by-claim basis based on the disclosure in the priority applications." *Lucent Technologies, Inc. v. Gateway, Inc.*, 543 F.3d 710, 718 (Fed. Cir. 2008). To receive benefit of a previous application, *every feature* recited in a particular claim at issue must be described in the prior application. *See In re van Langenhoven*, 173 USPQ 426, 429 (CCPA 1972) ("[T]he fact that *some* of the elements of the breech claims have support of the parent and foreign applications does not change the result. *As to given claimed subject matter, only one effective date is applicable.*" (emphases added)); *accord In re Chu*, 66 F.3d 292, 297 (Fed. Cir. 1995). As the Federal Circuit has noted, however, "[i]n order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter

at issue." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). Rather, "the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

With regard to enablement, an earlier application satisfies the enablement requirement if a relevant skilled artisan, after reading the disclosure could practice the invention recited in the later patent without undue experimentation. *In re Wands*, 858 F.2d 731, 736–37 (Fed. Cir. 1988). "[T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.'" *PPG Indus., Inc. v. Guardian Indus., Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996) (quoting *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984)). Moreover, "a patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

1. Claims 2 and 4

Petitioner contends that the priority date for claims 2 and 4 "is no earlier than the November 9, 1999 filing date of the '347 application." Pet. 15. Patent Owner responds that these claims are entitled to a priority date of November 9, 1998. Prelim. Resp. 9–11, n.4.

Claim 2 depends from claim 1 and additionally requires that the recited method of treatment include the administration of a chemotherapeutic regimen. Ex. 1001, 8:22–23. Claim 4 depends from claim 2 and recites that the chemotherapeutic regimen comprises cyclosphosphamide [sic]. *Id*. at 8:26–27.

We determine, for purposes of this decision that claims 2 and 4 are entitled to a priority date of November 9, 1998.

As Petitioner acknowledges (Pet. 16), the ’658 provisional application discloses that a “particularly preferred chemotherapeutic regimen that may be used in conjunction with the subject antibody immunotherapy comprises CHOP immunotherapy, which comprises the administration of a combination of cyclophosphamide, doxorubicin, vincristine and prednisone.” Ex 1002, 010. Similarly, the ’658 provisional application teaches that “[t]reatment of hematologic malignancy, such as CLL, B-PLL and transformed non-Hodgkin's lymphoma, according to the invention will comprise the administration of a therapeutically effective amount of an anti-CD20 antibody, which administration may be effected alone or in conjunction with other treatment(s), e.g., chemotherapy.” *Id*. at 006. In addition, the ’658 provisional application explains that “[p]revious reported therapies involving anti-CD20 antibodies have involved the administration of a therapeutic anti-CD20 antibody either alone or in conjunction with a second radiolabeled anti-CD20 antibody, or a chemotherapeutic agent.” *Id.* at 004. These disclosures reasonably convey to those of skill in the art that

the inventors had possession of the claimed subject matter as of November 9, 1998.

Furthermore, to the extent Petitioner asserts that the ’658 provisional application does not enable claims 2 and 4, we agree with Patent Owner that Petitioner’s unsupported, conclusory allegations are insufficient to establish, for purposes of this decision, that the ’658 provisional application fails to enable those claims. *See* Prelim. Resp. 10. As an initial matter, we note that although Petitioner asserts that claims 2 and 4 “lack written description or enablement support in the ’658 provisional application” (Pet. 21), Petitioner does not offer any evidence to support a conclusion that those claims are not enabled by that application. Indeed, neither Petitioner nor Dr. Andreeff alleges that undue experimentation would be required for an ordinarily skilled artisan in possession of the ’658 provisional application to practice the invention of claims 2 and 4. Moreover, as explained above, the ’658 provisional application discusses the treatment of CLL patients with rituximab and chemotherapy, including, in particular, the use of cyclophosphamide in such treatment (Ex. 1002, 006, 010), and describes studies in which rituximab and chemotherapy were co-administered (*id*. at 004). In view of these disclosures, we are unpersuaded, for purposes of this decision, by Petitioner’s assertion that claims 2 and 4 are not enabled by the ’658 provisional application.

2. Claim 3

Petitioner asserts that the priority date for claim 3 "is no earlier than the November 9, 1999 filing date of the '347 application." Pet. 15. Patent Owner disagrees. Prelim. Resp. 9–11, n.4.

Claim 3 depends from claim 2 and further requires that the chemotherapeutic regimen comprises fludarabine. Ex. 1001, 8:24–25.

We agree with Petitioner that claim 3 is not entitled to the November 9, 1998 filing date of the '658 provisional application. Although, as explained above, the '658 provisional application discloses the treatment of CLL patients with rituximab and chemotherapy (*see, e.g.*, Ex. 1002, 006), the '658 provisional application nowhere describes the use of fludarabine as a chemotherapeutic agent in such treatment. Further, in its Preliminary Response, Patent Owner does not explain why an ordinarily skilled artisan would have understood the applicant to have been in possession of a CLL treatment comprising administration of rituximab and fludarabine. Accordingly, on this record, we agree with Petitioner that claim 3 is entitled to a priority date of no earlier than November 9, 1999.

3. Claims 6 and 7

Petitioner contends that claims 6 and 7 "lack written description or enablement support in either the '658 provisional application or the '347 application" (Pet. 21) because "[b]i-weekly and monthly dosing are not discussed anywhere in the context of treating CLL" (*id.* at 22). Patent Owner disagrees. Prelim. Resp. 9–10, 11–14.

Claims 6 and 7 respectively require that the rituximab is administered "bi-weekly" and "monthly." Ex. 1001, 8:30–33.

We find no merit in Petitioner's contentions. The '658 provisional application describes bi-weekly and monthly rituximab dosing in the context of the "administration of a therapeutic anti-CD20 antibody" to treat "hematologic malignancies and, in particular, those characterized by high numbers of tumor cells in the blood." Ex. 1002, 005. The '658 provisional application expressly states that "[t]hese malignancies include, in particular, CLL" (*id.*) and that anti-CD20 antibody "administration may be effected by various protocols, e.g., weekly, bi-weekly, or monthly, dependent on the dosage administered and patient response" (*id.* at 009). Accordingly, we find the '658 provisional application to adequately disclose the subject matter of claims 6 and 7. *See Ariad*, 598 F.3d at 1351 ("the test for [written description] sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.").

Furthermore, to the extent Petitioner asserts that the '658 provisional application does not enable claims 6 and 7, we agree with Patent Owner that Petitioner's unsupported, conclusory allegations are insufficient to establish, for purposes of this decision, that the '658 provisional application fails to enable those claims. *See* Prelim. Resp. 10. In this regard, we note that, as with claims 2 and 4 discussed above, Petitioner does not offer any evidence to support a conclusion that claims 6 and 7 are not enabled by the '658 provisional application. Indeed, neither Petitioner nor Dr. Andreeff

alleges that undue experimentation would be required for an ordinarily skilled artisan in possession of the ’658 provisional application to practice the invention of claims 6 and 7. Moreover, as explained above, the ’658 provisional application discusses bi-weekly and monthly rituximab administration. Ex. 1002, 009. In view of these disclosures, we are unpersuaded, for purposes of this decision, by Petitioner’s assertion that claims 6 and 7 are not enabled by the ’658 provisional application.

Accordingly, we determine, for purposes of this decision, that claims 6 and 7 of the ’711 patent are entitled to a filing date of November 9, 1998.

4. Claim 9

Petitioner argues that claim 9 is entitled neither to the November 9, 1998 filing date of the ’658 provisional nor the November 9, 1999 filing date of the ’347 application. Pet. 19–23. With regard to the ’347 application, Petitioner contends that application lacks sufficient written description support for claim 9 of the ’711 patent. *Id.* Patent Owner responds that claim 9 is entitled at least to a priority date of November 9, 1999. Prelim. Resp. 9–10, 15, n.5.

Claim 9 recites, *inter alia*, a method of treating CLL comprising the administration of rituximab and a chemotherapeutic regimen comprising fludarabine and cyclophosphamide. Ex. 1001, 8:36–43.

We determine that, for purposes of this decision, claim 9 is entitled to a priority date of November 9, 1999. In addition to the disclosures concerning the combination of rituximab and chemotherapy discussed above with regard to the ’658 provisional application, the ’347 application

includes, as Example 5, a "Combination Antibody and Chemotherapy Protocol" (Ex. 1004, 050–052 (emphasis omitted)). In that Example, the '347 application explains that "[a]ntibody treatment of CLL can be combined with other conventional chemotherapeutic treatments known to be useful for the treatment of CLL." *Id*. at 051. Notably, Example 5 identifies both "single agent" chemotherapies and chemotherapeutic "drug combinations" as useful to treat CLL. *Id.* Furthermore, Example 5 identifies both cyclophosphamide and fludarabine as drugs useful in treating CLL. *Id.*; *see also id*. at 054 (original claim 11).

Petitioner acknowledges these disclosures, but nevertheless argues the '347 application fails to show that the inventors were in possession of "the combined use of cyclophosphamide, fludarabine, and rituximab" because that combination does not appear *in haec verba* in the application. Pet. 22. Petitioner's attempt to require the '347 application to provide *in haec verba* support for the claimed subject matter is not well taken. *See Purdue Pharma*, 230 F.3d at 1323; *see also Ariad*, 598 F.3d at 1352 (written description need not be in any particular form or an *in haec verba* recitation of the claimed invention). Indeed, in addition to improperly discounting the above described disclosures of the '347 application, Petitioner's priority date contentions are inconsistent with its position that the combination of cyclophosphamide and fludarabine was itself already a well-known chemotherapeutic regimen for treating CLL. *See, e.g.*, Pet. 40. "[T]he patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before."

Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1366 (Fed. Cir. 2006). Accordingly, in view of the express disclosures of the '347 application, and the knowledge of an ordinarily skilled artisan at the time that application was filed, we determine, for purposes of this invention, that claim 9 of the '711 patent is entitled to a priority date of no later than November 9, 1999.

C. Level of Ordinary Skill in the Art

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

According to Petitioner, a person of ordinary skill in the art at the time of the invention would have been "a practicing physician specializing in hematology or oncology, with at least three years of experience in treating patients with hematological malignancies." Pet. 26 (citing Ex. 1005 ¶ 18); *see also* Ex. 1002 ¶ 18. Patent Owner does not address Petitioner's position on this matter and does not propose its own description for a person of ordinary skill in the art at the time of the invention.

At this stage in the proceeding, we determine that Petitioner's description of the level of ordinary skill in the art is supported by the current record. Moreover, we have reviewed the credentials of Dr. Andreeff (Ex. 1005, Exhibit A) and, at this stage in the proceeding, we consider him to be qualified to opine on the level of skill and the knowledge of a person of

ordinary skill in the art at the time of the invention. We also note that the applied prior art reflects the appropriate level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

D. Anticipation by MD Anderson Newsletter

Petitioner asserts that claim 1 is anticipated under § 102 by the MD Anderson Newsletter. Pet. 26–29, 34–37. Patent Owner disagrees. Prelim. Resp. 29–38, 42–43.

1. MD Anderson Newsletter

The MD Anderson Newsletter discloses a clinical trial of rituximab in relapsed CLL patients. Ex. 1006, 004. The MD Anderson Newsletter explains that "[t]he B-cell antigen CD20 is expressed in 97% of cases of CLL. Therefore CLL should be an excellent target disease for the use of the IDEC antibody." *Id*.

The MD Anderson Newsletter notes that "CLL patients have a significant amount of disease in the blood which may bind with most of the administered IDEC," and accordingly suggests that "higher doses and/or more frequent exposure may be useful in CLL." *Id*. The MD Anderson Newsletter discloses the following rituximab dosage protocol: "the first dose would be 375 mg/m2 (about 6 hour infusion) but all subsequent doses would be higher, starting with 500 mg/m2 and escalating by 33% with subsequent patients." *Id*.

2. Discussion

Petitioner contends that the MD Anderson Newsletter anticipates claim 1 of the '711 patent because it describes a study in which relapsed CLL patients are to be treated with rituximab, and teaches rituximab doses of 500 mg/m^2. Pet. 34–37. Relying on the testimony of Dr. Andreeff, Petitioner asserts that MD Anderson Newsletter was publically accessible before the November 9, 1998 priority date of claim 1.[2] Pet. 26–29 (citing Ex. 1005 ¶¶ 69–75).

Patent Owner responds that the MD Anderson Newsletter cannot qualify as a printed publication because Petitioner has not established a reasonable likelihood that the newsletter was publicly accessible before the November 9, 1998 priority date of claim 1.[3] Prelim. Resp. 29–38. Patent Owner contends, therefore, that the MD Anderson Newsletter does not anticipate the challenged claim. *Id*. at 42.

The Federal Circuit has held that "public accessibility" is "the touchstone" in determining whether a reference is a printed publication. *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986). "A given reference is 'publicly accessible' upon a satisfactory showing that such document has

---

[2] Petitioner relies on the same arguments to support its contention that the MD Anderson Newsletter was publicly available before the November 9, 1999 filing date of the '347 application. Pet. 26–29.

[3] Patent Owner offers the same arguments against public accessibility of the MD Anderson Newsletter regardless of whether the November 9, 1998 filing date of the '658 provisional application or the November 9, 1999 filing date of the '347 application applies. Prelim. Resp. 29–38.

been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)).

Having considered the evidence of record, we determine that Petitioner has failed to establish that MD Anderson Newsletter was sufficiently accessible to the public before the priority date of claim 1.

Petitioner contends that the MD Anderson Newsletter was available both online (Ex. 1006) and in print (Ex. 1061) before the priority date of claim 1. Pet. 26–29. Although Petitioner relies on the online version of the newsletter to support its unpatentability contentions, it references the purported availability of the print version to buttress its position that the MD Anderson Newsletter was publicly accessible. *Id*.

Petitioner asserts that MD Anderson Newsletter appears in the Internet Archive Wayback Machine beginning February 8, 1999. *Id.* at 27. Petitioner submits an affidavit of Christopher Butler (Ex. 1056), Office Manager of the Internet Archive, in San Francisco, California, which is the creator of the Wayback Machine service. Pet. 27–28; Ex. 1056 ¶ 3. Attached to the Butler Affidavit is Exhibit A, which includes "true and accurate copies of printouts of the Internet Archive's records of the HTML files for the URLs and the dates specified in the footer of the printout." Ex. 1056 ¶ 6. Moreover, the Butler Affidavit explains how the date of the webpage can be determined from the URL. Ex. 1056 ¶ 5. Exhibit A to the

Butler Affidavit shows that the webpage disclosing MD Anderson Newsletter was archived on February 8, 1999. Based on this evidence, we are satisfied that the MD Anderson Newsletter was available on the website www.mdanderson.org as of February 8, 1999.

The availability of a reference on a website does not end the public accessibility inquiry, however. "When considering whether a given reference qualifies as a prior art 'printed publication,' the key inquiry is whether the reference was made 'sufficiently accessible to the public interested in the art' before the critical date." *Voter Verified, Inc. v. Premier Election Sols., Inc.*, 698 F.3d 1374, 1380 (Fed. Cir. 2012) (quoting *In re Cronyn*, 890 F.2d 1158, 1160 (Fed.Cir.1989)). "[E]vidence that a query of a search engine before the critical date, using any combination of search words, would have led to the [reference] appearing in the search results" is probative of public accessibility. *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1350 (Fed. Cir. 2016). Absent such evidence of indexing, various additional factors, including testimony indicating that the particular online publication in question was well-known to the community interested in the subject matter of the reference, and the existence of numerous related articles located within the same publication can support a determination of public accessibility. *See Voter Verified*, 698 F.3d at 1380–81.

In this respect, Petitioner's position is deficient. Petitioner relies on the Declaration of Dr. Andreeff to support its contention that MD Anderson Newsletter was publicly accessible by November 9, 1998. *See* Ex. 1005 ¶¶ 77–85. Dr. Andreeff testifies that

> [i]n 1998, doctors with patients seeking treatment for CLL routinely turned to MD Anderson to inquire about our ongoing clinical trials and the potential for their patients to be referred to MD Anderson for treatment as part of the trial. As part of this process, the Newsletter was disseminated to referring physicians, and they were free to share the information with their prospective patients.

Ex. 1005 ¶ 73. Dr. Andreeff further testifies that "[t]he physicians participating in the study, including myself, were [] especially motivated to spread the word about the Newsletters . . . to enroll more patients and thereby ensure the trial's success, and would have discussed the trial with referring doctors with CLL patients." *Id.* ¶ 74.

Absent from Dr. Andreeff's testimony, however, is any indication that he, or anyone else, in fact accessed the MD Anderson Newsletter. Dr. Andreeff does not, for example, provide evidence as to the number of page views for the MD Anderson Newsletter, or demonstrate that the newsletter was indexed or otherwise available via search engines during the relevant time. Nor does Dr. Andreeff testify that the MD Anderson Newsletter itself (as contrasted with the MD Anderson Cancer Center) was well-known to the community interested in the subject matter of that reference, or that numerous related articles were located within the same online publication. Furthermore, even crediting Dr. Andreeff's testimony that he and his colleagues were "especially motivated to spread the word" and "would have discussed the trial" (*id.*), absent from that testimony is any indication that Dr. Andreeff or his colleagues did in fact discuss the edition of the MD Anderson Newsletter relied upon in this proceeding with another

physician, or direct anyone to that newsletter. In addition, it is unclear from Dr. Andreeff's testimony what version of the newsletter purportedly would have been discussed with and disseminated to referring physicians, the online version presently asserted as prior art, or the print version, which is not independently proffered as anticipating claim 1. Stated plainly, there is insufficient evidence to show "that a person of ordinary skill interested in [the relevant technology] would have been independently aware of [the online publication] as a prominent forum for discussing such technologies." *Voter Verified*, 698 F.3d at 1380–81.

Similarly, to the extent Petitioner seeks to rely on Dr. Andreeff's testimony that "MD Anderson printed and distributed a Summer 1998 issue of the Leukemia Insights Newsletter" (Ex. 1005 ¶ 70), which was purportedly "mailed out to several thousand referring Hematology-Oncology physicians in the United States" (*id.* ¶ 71) to support its contention that the MD Anderson Newsletter was publicly accessible, we observe that such testimony is based not on Dr. Andreeff's firsthand knowledge, but on his conversations with Sherry Pierce, R.N., who herself has not submitted a declaration in this matter. Moreover, we note that Dr. Andreeff does not testify as to when MD Anderson Newsletter was actually published. Ex. 1005 ¶ 70. Nor does Dr. Andreeff direct us to any corroborating document supporting the contention that the MD Anderson Newsletter was published in or around the "Summer" of 1998. *Id.* In addition, even assuming that the MD Anderson Newsletter was published at that time, such

testimony does not show that the newsletter was then sufficiently accessible to members of the interested public.

Accordingly, in view of the above, we conclude that Petitioner has failed to establish that MD Anderson Newsletter was publically accessible as of the critical date of November 9, 1998.[4] Thus, on this record, MD Anderson Newsletter fails to qualify as prior art under 35 U.S.C. § 102, and Petitioner cannot establish the anticipation of claim 1 based on that reference.

E. Anticipation by Keating

Petitioner contends that Keating anticipates claims 7 and 9 of the '711 patent. Pet. 29, 37–39. Patent Owner disagrees. Prelim. Resp. 38, 43.

1. Keating

Keating is a 2005 article in the Journal of Clinical Oncology that discloses a clinical trial of a chemoimmunotherapy program consisting of fludarabine, cyclophosphamide, and rituximab. Ex. 1064, 006. With regard to rituximab dosing, Keating discloses that patients received 375 mg/m^2 rituximab on day 1 of the first cycle of treatment, and 500 mg/m^2 rituximab on day 1 of subsequent cycles given every 4 weeks for 6 total treatment

[4] Because the above-described deficiencies in Petitioner's public accessibility argument apply, for the reasons set forth above, we likewise conclude that Petitioner has not shown that the MD Anderson Newsletter was publicly accessibility as of the November 9, 1999 critical date of claims 3 and 9.

cycles. *Id*. at 007. Keating reports a 70% complete response rate, which "is the highest rate reported for initial therapy for CLL" and "supports the concept of additive or synergistic interactions of these three agents." *Id.* at 013.

2. Discussion

As set forth above, Petitioner has not established that claim 7 is not entitled to the November 9, 1998 filing date of the '658 provisional application, or that claim 9 is not entitled to the November 9, 1999 filing date of the '347 application. Furthermore, Petitioner acknowledges that Keating was not published until June 2005. Pet. 29. Accordingly, on this record, Keating fails to qualify as prior art under 35 U.S.C. § 102 to each of those claims. Therefore, we conclude that Petitioner has not demonstrated a reasonable likelihood that it would prevail in establishing that Keating anticipates claims 7 and 9.

F. Obviousness over Keating and MD Anderson Newsletter

Petitioner asserts that claim 6 is unpatentable under § 103 as obvious in view of the combination of Keating and the MD Anderson Newsletter. Pet. 26–29, 39–40. Patent Owner disagrees. Prelim. Resp. 29–38, 43–44.

As discussed above, Petitioner has not established that claim 6 is not entitled to the November 9, 1998 filing date of the '658 provisional application. Thus, on this record, each of Keating and the MD Anderson Newsletter fails to qualify as prior art under 35 U.S.C. § 102 to that claim. Accordingly, we conclude that Petitioner has not demonstrated a reasonable

likelihood that it would prevail in establishing that the cited combination renders obvious claim 6.

G. Obviousness over MD Anderson Newsletter and Byrd

Petitioner asserts that claims 2–4 and 9 are unpatentable under § 103 as obvious in view of the combination of the MD Anderson Newsletter and Byrd. Pet. 26–29, 40–47. Patent Owner disagrees. Prelim. Resp. 29–38, 44–48.

1. Byrd

Byrd describes a variety of established and emerging CLL therapies. Ex. 1010, 003. In particular, Byrd discloses clinical studies of treating CLL patients with combination therapies, including fludarabine and cyclophosphamide, as well as fludarabine and rituximab. *Id*. 006.

With regard to fludarabine and cyclophosphamide combination therapy, Byrd reports that such co-therapy yields "promisingly high response rates" for previously untreated CLL patients, and "impressive activity in both previously untreated and fludarabine-refractory individuals." *Id*. Byrd surmises that such results "suggest synergistic interaction between alkylator agents and fludarabine combination." *Id*.

Concerning the combination of fludarabine with rituximab, Byrd discloses that "[b]ecause of *in vitro* data suggesting that IDEC-C2B8 can chemosensitize chemotherapy-resistant NHL cell lines and the absence of competing toxicities, a study of interdigitated IDEC-C2B8 with [cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and

prednisone/prednisolone ("CHOP")] chemotherapy in relapsed low-grade NHL was initiated and recently completed noting an overall response rate of 100%." *Id*. Byrd further discloses that "a phase II/III study of fludarabine + IDEC-C2B8 in untreated CLL patients" is being planned. *Id*.

2. Discussion

As discussed above, Petitioner has not established either that claims 2 and 4 are not entitled to the November 9, 1998 filing date of the '658 provisional application, or that claims 3 and 9 are not entitled to the November 9, 1999 filing date of the '347 application. Thus, on this record, for the reasons set forth in Part II.D.2., above, the MD Anderson Newsletter fails to qualify as prior art under 35 U.S.C. § 102 to those claims. Furthermore, because Byrd, which does not disclose any dosage protocol for rituximab, is not relied upon to, and indeed fails to remedy the deficiencies arising from the unavailability of the MD Anderson Newsletter as prior art, we conclude that Petitioner has not demonstrated a reasonable likelihood that it would prevail in establishing that the cited combination renders obvious claims 2–4 and 9.

H. Obviousness over MD Anderson Newsletter, Byrd, and Kipps

Petitioner asserts that claims 6 and 7 are unpatentable under § 103 as obvious in view of the combination of the MD Anderson Newsletter, Byrd, and Kipps. Pet. 26–29, 47–52. Patent Owner disagrees. Prelim. Resp. 29–38, 48–52.

1. Kipps

Kipps discloses several chemotherapeutic regimens for the treatment of CLL. Ex. 1055, 034. For example, Kipps teaches that the following chemotherapeutic agents and dosage frequencies are useful to treat CLL: chlorambucil administered every 2–4 weeks; cyclophosphamide administered daily or every 3–4 weeks; chlorambucil and prednisone administered every 2–4 weeks; and fludarabine administered every 3–4 weeks. *Id*. at 034–035.

2. Discussion

As discussed above, Petitioner has not established that claims 6 and 7 are not entitled to the November 9, 1998 filing date of the '658 provisional application. Thus, on this record, MD Anderson Newsletter fails to qualify as prior art under 35 U.S.C. § 102 to those claims. Furthermore, because Byrd and Kipps fail to remedy the deficiencies arising from the unavailability of the MD Anderson Newsletter as prior art, we conclude that Petitioner has not demonstrated a reasonable likelihood that it would prevail in establishing that the cited combination renders obvious those claims.

I. Obviousness over FDA Transcript, Batata, and Maloney

Petitioner asserts that claim 1 is unpatentable under § 103 as obvious in view of the combination of the FDA Transcript, Batata, and Maloney. Pet. 30, 52–63. Patent Owner disagrees. Prelim. Resp. 38–42, 52–63.

1. FDA Transcript

The FDA Transcript covers a July 25, 1997 public hearing of the FDA Biological Response Modifiers Advisory Committee discussion of rituximab (IDEC-C2B8) between the FDA and representatives of IDEC Pharmaceuticals, including Dr. Antonio Grillo-Lopez and Dr. Christine A. White, both named inventors of the '711 patent. Ex. 1007, 020. During the hearing, Dr. Grillo-Lopez described a study involving treating patients having low-grade or follicular non-Hodgkin's lymphoma with rituximab, including IWF Type A patients. *Id.* at 037, 045. Dr. Grillo-Lopez explains that IWF Type A patients had a treatment response rate of 11%. *Id* at 044.

2. Batata

Batata discloses "[a] systematic comparison of the membrane phenotypes" in CLL and small lymphocytic lymphoma ("SLL"). Ex. 1008, 002. Batata concludes that "systematic comparison of surface markers between CLL and SLL demonstrated an almost identical phenotype, thus providing the evidence that they are different tissue expression of the same disease." *Id*. at 008.

3. Maloney

Maloney describes a dose escalation study to ascertain the toxicity of rituximab in human patients. Ex. 1009 at 003. Patients with relapsed low-grade B-cell non-Hodgkin's lymphoma, including one SLL patient, received a single intravenous infusion of up to 500 mg/m^2 rituximab. *Id.* at 005–006. All tested doses were well tolerated, including the 500 mg/m^2

dose, and "no dose-limiting toxicities were identified," though some infusion-related side effects were observed. *Id*. at 009.

4. Discussion

Petitioner asserts that the combination of the FDA Transcript, Batata, and Maloney renders obvious claims 1 and 5–8 of the '711 patent. Pet. 30, 52–63. In particular, Petitioner relies on the FDA Transcript, which describes a clinical trial of rituximab to treat IWF Type A low-grade non-Hodgkin's lymphoma patients as disclosing the administration of rituximab in an amount effective to treat CLL in human patients. *See id.* at 55–56. Petitioner additionally relies on Batata as disclosing that CLL and SLL are different tissue expressions of the same disease (*id.* at 54–56), and points to Maloney as teaching that 500 mg/m^2 is an effective, well-tolerated rituximab dosage amount for patients having relapsed low-grade non-Hodgkin's lymphoma (*id.* at 55–57).

Patent Owner responds, among other things, that Petitioner fails to establish that the FDA Transcript qualifies as prior art to the '711 patent. Prelim. Resp. 38–42. Patent Owner thus argues that the cited combination cannot render obvious claims 1 and 5–8. *Id*. at 52.

Having considered the evidence of record, we agree with Patent Owner that Petitioner has failed to establish that the FDA Transcript was sufficiently available to the public to constitute a printed publication. Petitioner relies upon a letter from Dynna Bigby from the Division of Dockets Management ("DDM") (Ex. 1054) at the FDA to support its contention that FDA Transcript is a prior art printed publication. Pet. 30.

According to Petitioner, the letter establishes that (a) the FDA Transcript would have been received on August 8, 1997, the date stamped on the FDA Transcript; (b) the DDM would have made the document publicly available via the DDM Public Reading Room; and (c) access to the FDA Transcript would have required filling out a reading room request form for the document. *Id*. Even if each of those assertions were taken as true, the record is missing a supported explanation that such availability of the FDA Transcript was in a manner and to an extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence would have been able to locate it. In other words, Petitioner has not explained how such persons may have known that the document existed and was available, upon request, in the DDM Public Reading Room. Without that information, Petitioner has not shown that the FDA Transcript is a prior art printed publication.

Consequently, the FDA Transcript is unavailable as prior art to support the contention that claims 1, and 5–8 are obvious. Furthermore, because Batata, which compares the membrane phenotypes of CLL and SLL, and Maloney, which describes a rituximab toxicity study, are not relied upon, and in fact fail to remedy the deficiencies arising from the unavailability of the FDA Transcript as prior art, we conclude that Petitioner has not demonstrated a reasonable likelihood that it would prevail in establishing that the cited combination renders obvious claims 1 and 5–8.

III. CONCLUSION

For the foregoing reasons, we conclude that the information presented in the Petition does not establish a reasonable likelihood that Petitioner would prevail in showing that claims 1–9 of the ’711 patent are unpatentable.

IV. ORDER

In consideration of the foregoing, it is

ORDERED that the Petition is DENIED and no trial is instituted.

PETITIONER:

Michelle S. Rhyu
James Brogan
Alla Brukman
COOLEY LLP
rhyums@cooley.com
jbrogan@cooley.com
abrukman@cooley.com

PATENT OWNER:

Michael R. Fleming
Gary N. Frischling
Keith A. Orso
Yite John Lu
David Gindler
IRELL & MANELLA LLP
mfleming@irell.com
gfrischling@irell.com
korso@irell.com
yjlu@irell.com
dgindler@irell.com