UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.

Petitioner,

v.

BIOGEN INC. AND GENENTECH, INC.

Patent Owners.

Case IPR2017-02126
U.S. Patent No. 7,682,612

PATENT OWNERS' PRELIMINARY RESPONSE

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TABLE OF CONTENTS

Page

Page

Page

Page

TABLE OF AUTHORITIES

Page(s)

Cases

Page

Page

Statutes

Rules

Other Authorities

I. INTRODUCTION

The claims of U.S. Patent 7,682,612 (the "'612 patent") describe methods of treating chronic lymphocytic leukemia ("CLL") by administering rituximab, an anti-CD20 antibody, alone or combined with chemotherapy, in an amount effective to treat the chronic lymphocytic leukemia. Ex. 1001, 7:62-10:51. This is the third *inter partes* review petition filed against the '612 patent in less than a year, the first two being IPR2017-01227 and IPR2017-1230. Petitioner here challenges the claims of the '612 patent on three grounds. Because Petitioner has failed to carry its burden to show that any claim of the '612 patent is unpatentable, the Board should deny institution here on all grounds, just as it did in the prior IPRs.

Petitioner treats the "amount effective to treat the chronic lymphocytic leukemia" limitation in the claims as if it were "amount effective to deplete B cells." But the intrinsic evidence makes clear that the term "amount effective to treat the chronic lymphocytic leukemia" means more than that. According to the prosecution history, an amount effective to treat the CLL means an amount providing a positive clinical benefit to the CLL patient. Petitioner fails to establish that any claim of the '612 patent is obvious under a proper construction of the claims.

All three grounds in the petition rely on Ex. 1006, which Petitioner refers to as a "Genentech Press Release" allegedly posted to the Internet before the priority date. Institution should be denied on all three grounds because Petitioner fails to establish that Ex. 1006 is a prior art printed publication on which *inter partes* review may be based.

Petitioner also fails to establish that the prior art discloses each limitation of the claims, including administering to CLL patients an amount of rituximab effective to treat the CLL. Unable to identify any prior art disclosing the use of rituximab to treat CLL, Petitioner relies on references by Maloney et al. reporting studies in NHL. Petitioner does not contend that NHL and CLL are the same disease. Nor could it. CLL is a type of leukemia, for example, whereas NHL is a type of lymphoma. Maloney even highlights a significant difference between the cancerous cells of CLL and NHL—six-fold lower density of CD20 expression—that may significantly affect their responsiveness to rituximab treatment. Petitioner resorts to patchwork quotations from, and counterfactual interpretations of, the NHL references to try and support its positions, but the references simply do not suggest treating CLL patients with rituximab.

Even if the prior art did disclose the administration of rituximab to a CLL patient, Petitioner failed to show that the claimed methods of administering specific rituximab doses for treating CLL were obvious.

Petitioner's arguments revolve around the assertions that (i) 375 mg/m^2 was the "dose of choice" for NHL; (ii) CLL patients have 100 times more tumor cells than NHL patients; and (iii) the rituximab dose should be "proportional to the total number of tumors that need to be destroyed." Taken to its logical conclusion, Petitioner's argument would suggest a rituximab dose for CLL that is at least 100 times higher than that for NHL, or 37,500 mg/m^2. Such a dose is far greater than the doses of 375 mg/m^2 and 500 mg/m^2 that Petitioner relies upon in its challenge. Petitioner cites nothing in the prior art suggesting that a 100-fold ***increase*** in tumor cells having a six-fold ***lower*** density of CD20 expression relative to NHL could be accounted for by at most a mere 33% increase in the "dose of choice" for NHL from 375 mg/m^2 to 500 mg/m^2 of the anti-CD20 antibody rituximab. Petitioner arrives at doses of 375 mg/m^2 and 500 mg/m^2 based solely on hindsight.

Petitioner also failed to establish any reasonable expectation of success. First, Petitioner's expectation-of-success arguments rely on Ex. 1006, "the Genentech Press Release," which Petitioner failed to qualify as a prior art printed publication. Second, Petitioner contends that Ex. 1006 disclosed that Patent Owners were conducting clinical trials with CLL patients. But Ex. 1006 contains no such disclosure. Even if it did, the mere initiation of a clinical trial would not have established a reasonable expectation of success in treating CLL. Nor does Petitioner attempt to establish a reasonable expectation of

success under the proper construction of an "amount effective to treat the chronic lymphocytic leukemia."

Petitioner further argues that the claimed inventions were obvious to try, but these arguments are based on artificially-narrow universes of alleged "identified, predictable solutions" constructed by hindsight for each claim. Moreover, to establish that an invention was obvious to try, not only must there have been a finite number of identified, predictable solutions in the art, there must also have been a reasonable expectation of success, which Petitioner failed to show.

Additionally, Petitioner failed to show that a POSA would have been motivated to add chemotherapy to rituximab, or would have had a reasonable expectation of success in doing so. Petitioner contends that the lower density of CD20 expression on the B cells of CLL patients presented a "targeting" problem for an anti-CD20 antibody like rituximab, making it less likely that rituximab alone could successfully treat CLL. According to Petitioner, this would have prompted a POSA to combine rituximab with chemotherapy because rituximab-bound B cells were reportedly known to be chemosensitive. But adding chemotherapy would not have solved this targeting problem, because rituximab only would have chemosensitized those B cells that it happened to hit in the first place; Petitioner does not contend that

chemotherapy would have made rituximab any more likely to hit the targeted B cells.

For at least these reasons, and the reasons explained further below, the board should decline to institute *inter partes* review.

II. BACKGROUND

A. Chronic Lymphocytic Leukemia (CLL)

Chronic Lymphocytic Leukemia ("CLL") as its name implies, belongs to a group of cancers called leukemias. Ex. 2001, 003. Generally, leukemia is a "[c]ancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal [*i.e.*, cancerous] blood cells to be produced and enter the bloodstream." Ex. 2002, 001.

In CLL, the cancerous cell, as relevant here, is a type of white blood cell known as a "B lymphocyte," or "B-cell." Ex. 2001, 003. The cancerous B lymphocytes of CLL differ in kind from normal B lymphocytes (and from other types of cancerous B lymphocytes). For example, the B lymphocytes of CLL display lower levels of a cell-surface antigen called "CD20." *See* Ex. 1004, 6. Indeed, it was known in the art that this "dim CD20 expression is a unique feature" of the B-cells in CLL as compared to those in normal peripheral blood or in low-grade NHL ("LG-NHL") patients. Ex. 2003, 005. Quantitatively, CD20 is expressed on the surfaces of CLL

B cells at about one-sixth the density that it is expressed on the B cells of LG-NHL patients. *Id.* at 002 (Table 1).

The cancerous B lymphocytes of CLL differ from other B lymphocytes not only in kind, but also in number. In CLL, cancerous B lymphocytes proliferate and accumulate in the blood, leading to lymphocyte levels in CLL patients that are much higher than those found in other people. Ex. 2001, 004-005. A healthy person, for example, generally has no greater than 4,500 circulating lymphocytes per microliter of blood ("4,500 lymphocytes/μL"). *Id.* As another example, the low-grade lymphoma patients in Maloney 1994 had fewer than 2,500 B lymphocytes/μL before treatment. *See* Ex. 1003, 7 (Table 3). A CLL patient, by contrast, typically has a much greater number—and therefore is said to have "lymphocytosis." Ex. 2001, 004. "[I]n most patients, the absolute lymphocytosis exceeds 15 x 10^9/L," *id.*, which is equivalent to 15,000 lymphocytes/μL.[1] As set forth in the National Cancer Institute-Sponsored Working Group Guidelines for CLL (the "NCI Guidelines For CLL"), at least 5,000 lymphocytes/μL is considered the ***minimum*** lymphocyte count for a CLL diagnosis. Ex. 2004, 003.

[1] Because there are one million (1 x 10^6) microliters (μL) in one liter (L), 1 x 10^9/L equals 1000/μL.

B. Development Of Treatments For CLL

While there were no proven cures for CLL in the 1990s, splenectomy, radiation therapy, stem cell transplantation, and various chemotherapies were used as treatments, with limited success. Ex. 2005, 033-036.

The inventors of the '612 patent conceived of new treatments for CLL using antibodies like rituximab, which bind to the CD20 antigen. Ex. 1001 at 1:29-35, 41-45. The inventors conceived of these treatments even though it was known that CLL is characterized by "dim CD20 expression."

Prior tests of rituximab in small lymphocytic lymphoma ("SLL") patients, whose B lymphocytes also express low levels of CD20, suggested that the inventors would be unsuccessful. Ex. 2006, 006; Ex. 1004, 6 (describing the lower expression of the CD20 surface antigen that has been observed in cases of CLL); Ex. 1002, ¶ 48 (Petitioner's expert agrees). For example, one of the references on which Petitioner relies in each of its grounds for challenge describes a trial of rituximab therapy for patients with low-grade NHL, including four SLL patients. Not one of the four SLL patients responded to treatment with rituximab even though observable responses were reported in the other NHL patients. Ex. 1004, 6. The investigators attributed these non-responses to the similarity in morphology between CLL and SLL cells, stating that rituximab may not have been effective "due to a lower expression of the CD20 surface antigen that has been observed in cases of CLL." *Id*.

III. CLAIM CONSTRUCTION

The Board should construe the phrase "amount effective to treat the chronic lymphocytic leukemia" to mean "amount providing a positive clinical benefit to the chronic lymphocytic leukemia patient."

A United States District Court previously construed an amount "effective to treat the chronic lymphocytic leukemia." *Biogen Idec, Inc. v. GlaxoSmithKline LLC*, No. 10-CV-00608-BEN BGS, 2011 WL 4949042, at *2-3 (S.D. Cal. Oct. 18, 2011). Acknowledging that "[t]he parties agree[d] that 'effective to treat the chronic lymphocytic leukemia' includes the amount of [rituximab] that achieves a reduction in circulating tumor cells," the Court explained that "the issue is whether a patient *must also* reach a positive clinical benefit in order for the treatment to be effective." *Id.* at *3. Guided by the prosecution history, the Court concluded that the answer is "yes." *Id.* at *4; Pet. 28 n.8. The prosecution history mandates the same conclusion here. *See D'Agostino v. MasterCard Int'l Inc.*, 844 F.3d 945, 948 (Fed. Cir. 2016).

A. According To The Prosecution History, An Amount Effective To Treat The CLL Means An Amount Providing A Positive Clinical Benefit To The CLL Patient.

As explained below, the term "effective to treat the CLL" was added to the claims during prosecution of the '612 patent to replace the phrase "effective to achieve a reduction in circulating tumor cells," and the applicants expressly

stated that the new phrase required a positive clinical benefit in the CLL patient.

Original claim 1 was directed to a "method of treating hematologic malignancy associated with high numbers of circulating tumor cells by administering a therapeutically effective amount of an anti-CD20 antibody or antigen binding fragment thereof, said amount being effective to achieve a reduction in circulating tumor cells." Ex. 2006, 002. In response to a rejection by the examiner, these claims were cancelled and replaced with claims specifically requiring the amount administered to be "effective to treat the chronic lymphocytic leukemia." Ex. 2007, 003-010.

The applicants explained that these new claims were specifically directed to a different goal: "The new claims also differ from the claims they replace in that the amount of anti-CD20 antibody administered to the patient is required to be 'effective to treat the chronic lymphocytic leukemia,' instead of 'effective to achieve a reduction in circulating tumor cells.'" *Id.* at 015.

"[C]laims are interpreted by reference to those that have been cancelled or rejected." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co*., 535 U.S. 722, 733 (2002). "[B]y the amendment [the patentee] recognized and emphasized the difference between the two phrases"—"effective to achieve a reduction in circulating tumor cells" and "effective to treat the chronic lymphocytic leukemia"—and elected the latter over the former. *Id.* "The

difference which [the patentee] thus disclaimed must be regarded as material." *Exhibit Supply Co. v. Ace Patents Corp.*, 315 U.S. 126, 137 (1942). Thus, "effective to treat the [CLL]" cannot merely mean "effective to achieve a reduction in circulating tumor cells."

In a 2009 response to the PTO, the applicants further explained that "effective treatment of CLL must result in a ***positive clinical benefit*** to the CLL patient. . . . ***[T]he claims do require a specific, positive therapeutic outcome, and not simply induction of any type of response in the patient***." Ex. 2008, 648 (emphasis added) (internal quotation marks omitted).

Along with this response, the applicants provided a declaration from Dr. David Schenkein, a practicing hematologist/oncologist at the time of the invention. Dr. Schenkein's declaration explained that "'an amount effective to treat the CLL' . . . . must result in a positive clinical benefit to the CLL patient." *Id.* at 541 (emphasis omitted). For example, treatments that "demonstrated efficacy with minimal infusion related toxicity, overall response rate (ORR), complete responses (CR), partial responses (PR), improved median time to progression or improved duration of response, or remission upon treatment." *Id.* (internal citations omitted).

The applicants also distinguished the claimed "effective[ness]" from the ineffective treatment described by Jensen (Ex. 1009). Ex. 2008, 540-541. Jensen is a "Rapid Communication" published in July/August 1998 reporting

that the administration of 375 mg/m^2 rituximab to a CLL-like patient resulted in "severe side effects," which the authors attributed to "rapid tumor lysis." Ex. 1009, 1-2. Three subsequent, weekly infusions were administered "without clinical problems," but, despite the initial normalization of the circulating lymphocyte count, the patient had progressive disease. *Id.* at 2. Progressive disease is considered "treatment failure." Ex. 2004, 008. Jensen warns that "[p]hysicians must be aware of this hitherto unreported phenomenon in patients with high CD20-positive blood counts." Ex. 1009, 2. Similarly disappointing results were reported for an additional six patients. *Id.* at 3. Serious side effects ("acute tumor lysis and NCI grade III and IV toxicities") were reported for five patients with high lymphocyte counts and no positive clinical efficacy data was reported for any of the six additional patients. *Id*. at 2. As the applicants explained, "the requirements of the claims are not met by Jensen, as by no measure can an undesirable and life-threatening condition in the CLL patient, coupled with a continued progression of the CLL disease be considered an effective treatment of CLL." Ex 2008, 648 (internal quotation marks omitted).

B. Petitioner Does Not Dispute That An Amount Effective To Treat The CLL Means An Amount Providing A Positive Clinical Benefit To The CLL Patient.

Petitioner acknowledges that in IPR2017-01230 and -1227, Patent Owner argued that "effective to treat the chronic lymphocytic leukemia" means "providing a positive clinical benefit to the chronic lymphocytic leukemia

patient." Pet. 24. Petitioner nowhere disputes this meaning. Instead, Petitioner argues that "[t]he ultimate construction of this claim term is not material to this petition" because "achieving a reduction in circulating CLL tumor cells is sufficient to provide a POSA with a reasonable expectation of a clinical benefit." *Id.* at 24. The Board should reject this argument.

Petitioner contends that reducing circulating CLL tumor cells would have been sufficient to provide a POSA with a reasonable expectation of a clinical benefit because Patent Owners allegedly argued during prosecution that "teaching that [500 mg/m^2 and 375 mg/m^2] doses of rituximab have the effect of reducing circulating tumor cells—is sufficient under 35 U.S.C. § 112 to support a claim for a positive clinical benefit for treating the CLL." Pet. 25. But Patent Owners made no such argument. Nor can any such argument be inferred from Patent Owners' amendment of the claims to require "an amount effective to treat the chronic lymphocytic leukemia."

Petitioner asserts that "the *only* specification support for using the claimed doses to achieve an amount effective to treat the CLL is Example 3" and that "Example 3 merely discloses that the claimed 500 mg/m^2 dose (after an initial 375 mg/m^2 dose) caused a 'reduction of peripheral blood lymphocytosis' in CLL patients, i.e., a reduction in circulating tumor cells." Pet. 25. But Example 3 is not the only specification support for using the claimed rituximab doses to achieve an amount effective to treat the CLL, and

the disclosure of Example 3 is not as limited as Petitioner suggests. Elsewhere, the specification explains, for example, that "[t]he invention involves the discovery that hematologic malignancies and, in particular, those characterized by high numbers of tumor cells in the blood may be effectively treated by administration of a therapeutic anti-CD20 antibody." Ex. 1001 at 2:16-19. The specification then describes various ranges of "[t]ypically effective dosages," *id.* at 3:48-54, and sets forth Example 3, which reports that according to the invention, eight "patients receive[d] a first dose of 375 mg/m^2 to minimize infusion related side effects," with "[s]ubsequent weekly dosages (3) . . . given at an increased dose level," including 500 mg/m^2, 650 mg/m^2 and 825 mg/m^2. *Id.* at 6:6-7, 22-23. Example 3 teaches that administration of rituximab according to the invention can provide a positive clinical benefit to the CLL patient, including "full remission." *Id*. at 23-24. Dr. Scheinkin affirmed the same during prosecution, with specific reference to Example 3. Ex. 1023, 9-10 (¶ 34) (citing this full "remission upon treatment (page 11, paragraph 0370)"[2] as an example of a positive clinical benefit of the invention).

Petitioner ignores the disclosure of "full remission" in Example 3 because the patent reports that the patient who achieved that result was "treated

[2] Paragraph 0370 of the specification corresponds to the second paragraph of Example 3. Ex. 2009, 011.

at 560 mg/m^2." But Petitioner does not dispute that even a dosage of 560 mg/m^2 is within the scope of the invention set forth in the specification and that Example 3 therefore discloses to a POSA that the invention, which also encompasses dosages of 500 mg/m^2, includes providing a positive clinical benefit to a CLL patient.

Petitioner's suggestion that Example 3 does not provide written description support for achieving a positive clinical benefit in a CLL patient using the claimed doses is contrary to law. "[T]he written description requirement does not demand either examples or an actual reduction to practice;" and it "does not demand any particular form of disclosure, or that the specification recite the claimed invention *in haec verba*." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351-52 (Fed. Cir. 2010).

IV. PETITIONER FAILED TO ESTABLISH THAT EX. 1006 ("THE GENENTECH PRESS RELEASE") IS A PRIOR ART PRINTED PUBLICATION

A patent claim can be challenged in *inter partes* review "only on the basis of prior art consisting of patents or printed publications." 35 U.S.C. § 311(b). "'[P]ublic accessibility' has been called the touchstone in determining whether a reference constitutes a 'printed publication' bar under 35 U.S.C. § 102(b)." *SRI Int'l Inc. v. Internet Sec. Sys., Inc*., 511 F.3d 1186, 1194 (Fed. Cir. 2008). "A given reference is 'publicly accessible' upon a satisfactory showing that such document has 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." *Id.* (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)).

Petitioner has not shown that Ex. 1006, the alleged "Genentech Press Release," or "Press Release," was a prior art printed publication.

A. Petitioner Failed To Establish That Ex. 1006 Was Actually Posted To The Internet By The Priority Date.

Petitioner contends that Ex. 1006 "was captured on the 'Internet Archive' on 13 June 1997, suggesting it was available on the Internet no later than that date." Pet. 28-29. To establish the Press Release's alleged publication date, Petitioner relies on the testimony of Dr. Bennett, the "Managing Partner of the firm Prior Art Documentation LLC." Ex. 1031, Appendix 1 (*curriculum*

vitae). Dr. Bennett testifies that the document alleged to be the Press Release was "an Internet Archive capture of Document 1, made on 13 June 1997, from a Genentech Web page." *Id*. at ¶ 40.

The only support Dr. Bennett offers for this proposition is general testimony regarding the alleged operation of the Internet Archive's "Wayback Machine." *Id*. at ¶¶ 27-32. However, Dr. Bennett does not offer any foundation for such testimony nor does he establish that he is competent to offer it. Dr. Bennett does not purport to have firsthand knowledge about past or present activities or capabilities of the Internet Archive organization. He does not claim to ever have worked there. He cites no source or support for his bald assertion that "[c]rawlers automatically create a snapshot of webpages as they existed at a certain point in time" and that "[t]he Wayback Machine is an application using a crawler created by the Internet Archive to search its archive of Web page URLs and to represent, graphically, the date of each crawler capture." Ex. 1031, ¶ 28. Nor does he cite any source or support for his assertion that "the URL for the capture begins with the identification of the Internet Archive page (*e.g*., http://web.archive.org/web/) followed by information that dates and time stamps the capture as follows: year in yyyy, month in mm, day in dd, time code in hh:mm:ss (*e.g.*, 20041208081749, or 8 December 2004 at 8:17:49 a.m.) . . . followed by the URL of the original capture site." *Id.* at ¶ 30. Notably, Ex. 1006 bears no "URL for the capture." Ex. 1006.

Dr. Bennett claims that "[t]he Internet Archive is a resource that is well known to library professionals and is used by many such professionals." Ex. 1031 at ¶ 32. But even assuming that is true, it does not establish library professionals are competent to testify as to what goes on—or allegedly has gone on—at the Internet Archive company, including the alleged activities or capabilities of Internet Archive crawlers.

Dr. Bennett can offer only speculation about the operation of the Internet Archive's "crawlers," and does not purport to have any knowledge about the alleged webpage of Ex. 1006. Thus, Petitioner has failed to meet its burden of establishing that Ex. 1006 is prior art to the '612 patent. *See ActiveVideo Networks, Inc. v. Verizon Commc'ns., Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012) (discounting expert testimony where the expert "never provided any factual basis for his assertions"); *Delphix Corp. v. Actifio, Inc.*, No. IPR2015-01678, Paper 8, at 20 (P.T.A.B Feb. 10, 2016) (denying institution where Petitioner relied on "conclusory expert testimony that, itself, does not cite to evidentiary support").

Petitioner relies on *IBM Corp. v. Intellectual Ventures II LLC*, No. IPR2015-00089, Paper No. 44, at 57 (P.T.A.B. Apr. 25, 2016) as allegedly holding that "Wayback Machine evidence" is sufficient to "determine that a Petitioner has shown that [a reference] was publicly available." Pet at 34. But that case is inapposite for at least two reasons. First, the holding on which

Petitioner relies addresses the ***admissibility*** of evidence in the context of a Motion to Exclude, not whether "Wayback Machine evidence" is ***sufficient*** to establish a particular publication date. *See IBM Corp*., Paper No. 44, at 50-57. Second, the "Wayback Machine evidence" in *IBM Corp.* was a "Butler Affidavit" from "the Office Manager of the Internet Archive, which includes the Wayback Machine service." *Id.* at 53-54. Here, by contrast, Petitioner offers only an unsupported declaration by Dr. Bennett, an individual unassociated with the Internet Archive. Accordingly, Petitioner fails to establish that Ex. 1006 is a prior art printed publication.

B. Petitioner Failed To Establish That Exhibit 1006 Would Have Been Either Discoverable Or Independently Known By A POSA.

Even assuming Ex. 1006 was posted on the internet and recorded by the Internet Archive's crawlers on the date alleged by Petitioner, Petitioner does not present evidence demonstrating that a POSA would have searched for or known how to locate any such post. Nor does Petitioner provide evidence that a POSA would have actually known of any such post before the priority date. The Petition and testimony from Drs. Bennett and Ozer fail to establish that an interested POSA would have been able to locate the Press Release, even with diligent effort. *Blue Calypso, LLC v. Groupon, Inc.,* 815 F.3d 1331, 1350 (Fed. Cir. 2016).

Dr. Bennett nowhere refers to Exhibit 1006. Instead, he refers to "Document 1" attached to his declaration. Dr. Bennett describes "Document 1" as a "news release issued on 16 March 1995 by Genentech, Inc." Ex. 1031, ¶ 39. Dr. Bennett asserts that "it is self-evident that Genentech, as joint manufacturer of Rituxan, would have wished to make Document 1 readily available to members of the medical community and others" and therefore "[t]he reasonable conclusion is that (1) Internet search engines in 1997 would have been able to find and index Document 1, and (2) that a person of ordinary skill in the art in 1997 using typical Internet search tools would have readily found a copy of Document 1." *Id.* at ¶ 40. This is a non sequitur, and the Board should reject it. Whether an Internet search engine would have been able to locate and index a document in the 1990s, and whether a POSA would then have been able to find the document on the Internet simply cannot be inferred from someone's presumed wishes regarding the document. Petitioner's attempt to substitute self-serving presumptions for evidence fails.

Dr. Bennett offers no testimony as to what internet search tools were available in the 1990s, whether and how a POSA would have used them, and whether the particular URL at which "Document 1" allegedly was found would have been located by one. As the Federal Circuit has held, the bare argument that "an internet search engine would have been able to locate" a document does not allow one to "automatically infer that . . . [the] webpage was 'indexed

. . . through search engines or otherwise' and thus locatable by a search engine." *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331. 1350 (Fed. Cir. 2016). Such an inference is particularly unwarranted in cases like this, where the "record is devoid of any evidence that a query of a search engine before the critical date, using any combination of search words, would have led to the [challenged document] appearing in the search results." *Id*. Dr. Bennett's conclusory assertion that a search engine would have found "Document 1" before the priority date is not enough.

Petitioner contends that "[r]egardless of whether Genentech's website was indexed through Internet search engines, Dr. Ozer explains that POSAs would have been independently aware of press releases issued by prominent companies undertaking clinical investigations of new cancer drugs, and would have specifically been aware of press releases from Patent Owners due to the collaboration between scientists and industry." Pet. 29. But that is not what Dr Ozer's declaration says. Rather, it simply says that "POSAs were routinely ***made aware*** of ongoing clinical studies and their results through the issuance of press releases on the part of companies involved in the investigation of new cancer therapies." Ex. 1002, ¶ 57 (emphasis added). Even if that were true, it would not establish that a POSA would have been aware of "Document 1" in particular, or that any such awareness would have preceded the priority date.

Without explanation or elaboration, Dr. Ozer asserts that "[t]his press release would have been widely disseminated to the community." *Id.* As an initial matter, Dr. Ozer does not testify that the alleged press release "was" widely disseminated. Rather, he testifies only that it "would have been" widely disseminated. In any event, proof of actual dissemination requires far more than bald assertions. *Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1330 (Fed. Cir. 2004) (finding that testimony regarding "general practice" is inadequate "evidence of actual availability" to support a finding that dissemination occurred). Dr. Ozer does not purport to have firsthand knowledge regarding whether the alleged press release was ever actually distributed to POSAs before the priority date. Nor does he testify that he himself viewed it before the priority date.

Dr. Ozer asserts that "in any case a POSA interested in ongoing clinical studies would have known how to search for it." Ex. 1002, ¶ 57. But Dr. Ozer does not identify how a POSA would have known that the alleged press release existed in the first place. Nor does he identify how a POSA allegedly would have searched for it, or that the POSA would have actually found it. A document is not a printed publication if it "was only available for 'viewing and downloading' to members of the public who happened to know that the [] paper was there." *Groupon, Inc. v. Blue Calypso LLC*, No. CBM2013-00044, 2014 WL 7273564, at *11 (P.T.A.B. Dec. 17, 2014) (internal citation omitted).

Dr. Ozer's testimony rests only on "assumptions, not facts" since he neither received the alleged press release via the dissemination channels he postulates existed, nor found the alleged press release before the priority date through the use of search tools. *AT&T Corp. v. Microsoft Corp.*, No. 01-4872C (WHP), 2004 WL 292321, at *6 (S.D.N.Y. Feb. 17, 2004). Thus, even if the alleged press release was posted to the internet by June 13, 1997, as alleged by Petitioner, the evidence still fails to establish that it is a printed publication because Petitioner fails to show that the document was discoverable or had actually been disseminated.

V. GROUND I: CLAIMS 1-13, 15-22, 58 AND 60 ARE NOT OBVIOUS OVER MALONEY 1994, MALONEY (SEPT.) 1997, AND THE "GENENTECH PRESS RELEASE"

A. Petitioner Failed To Establish That The Press Release Is A Prior Art Printed Publication.

Petitioner failed to establish that "the Genentech Press Release" was publicly available before the priority date, as discussed in Section IV. Accordingly, "the Genentech Press Release" does not "fall[] within the proper scope of an *inter partes* review," *Cisco Sys. v. Constellation Techs.*, No. IPR2014-01085, Paper 11, at 9 (P.T.A.B. Jan. 9, 2015), and Ground I fails.

B. Petitioner Did Not Show That The Prior Art Discloses "treating chronic lymphocytic leukemia (CLL) in a human patient" With Rituximab.

Petitioner relies on Maloney 1994 for this claim element, but Maloney 1994 did not suggest that rituximab could be used to treat CLL. According to Petitioner, "Maloney 1994 suggested that anti-CD20 antibodies (e.g., rituximab) could be useful therapies for both NHL and CLL cancers, because both diseases manifested in CD20-positive B-cells." Pet. 32. But Maloney 1994 never makes any such suggestion. If anything, it suggests the opposite because it contrasts NHL and CLL by pointing out that CD20 is "expressed at a lower density on B-cell chronic lymphocytic leukemia." Ex. 1003, 3. Petitioner plucks the phrase "B-cell chronic lymphocytic leukemia" from this statement of contrast and concatenates it with a sentence fragment that appears many lines earlier in the paper to manufacture the assertion that Maloney 1994 "taught that CD20 was 'present on the surface of nearly all B cells[,] provid[ing] a more universal target for immunotherapy'[[3]] than other antigens, in NHL patients as well as patients with

[3] In Maloney 1994, the sentence ends here, citing footnote reference 4.

'B-cell chronic lymphocytic leukemia.[4]'" Pet. 32 (citing Ex. 1003, 3). Maloney 1994 taught no such thing. Petitioner asserts that Maloney 1994 reported "dose-dependent, rapid, and *specific depletion of the B cells* in all patients." Pet. 32. But Petitioner itself admits that those patients were "low-grade NHL patients," not CLL patients whose disease is characterized by cancerous B cells that express CD20 at a lower density. *Id.*

Unable to point to any other mention of CLL in Maloney 1994, Petitioner argues that Maloney 1994 is actually referring to CLL indirectly when it states that "using multiple doses [of rituximab] to achieve prolonged, tumor-saturating levels may lead to responses in patients with more extensive disease." Pet. 32; Ex. 1003, 11. But contrary to Petitioner's assertions, the passing reference to "more extensive disease" refers to a higher number of large tumors in the LG-NHL patients studied by Maloney 1994, not to patients with a different disease altogether (CLL).

Maloney describes its lymphoma patients with multiple large tumors as having "extensive disease." Ex. 1003, 5, Table 1. Specifically, Maloney

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[4] This point is supported by footnote reference 8, which is Almasri 1992. *See* Ex. 2003 (describing lower density of CD20 on the B cells of CLL). The intervening three sentences citing supporting references 5, 6, and 7 are omitted from Petitioner's quote.

estimated "tumor bulk" for each of the fifteen lymphoma patients in the study based on "physical exam and CT scans of the chest, abdomen, and pelvis," and reported in the "Disease Bulk" column of Table 1 the grade for each patient as follows: "multiple areas of adenopathy [swollen lymph nodes] with largest mass < 5 cm (+), nodal mass > 5 cm (++), ***extensive disease with multiple areas > 5 cm (+++)***." *Id*., Table 1, n.†.

Along with "Disease Bulk," Table 1 also reports corresponding "Maximal Responses" from patients, providing the foundation for Maloney's subsequent statement about "[e]xtension of these studies." Ex. 1003, 11. As shown in the "Maximal Response" column of Table 1, the best result achieved by any patient was a partial response (PR). Two patients achieved PRs and one may have achieved a "Delayed PR." Ex. 1003, 5 (Table 1). All three of these patients had the lowest "Disease Bulk" in the studies, each rating only a "+". *Id.* None of the patients with greater "Disease Bulk"—more extensive disease—achieved a PR. In the "Discussion" section of the paper, Maloney observed that "[i]t is possible that longer duration of antibody therapy achieving saturating levels may also cause a greater antitumor effect," Ex. 1003, 10, and then concluded that "[e]xtension of these studies using multiple doses to achieve prolonged, tumor-saturating levels may lead to responses in patients with more extensive disease." *Id.* at 11. In other words, Maloney simply suggested that low-grade NHL patients with multiple larger

tumors (*e.g.* those with "Disease Bulk" grades of ++ or +++) might need more rituximab than those with fewer tumors (*e.g.*, those with "Disease Bulk" grades of +), the only patients in whom Maloney was seeing some success.

The discussion of antibody pharmacokinetics in Maloney 1994 also makes clear that "extensive disease" refers to the extent of LG-NHL, not to an entirely different disease like CLL. The paper explains that "it is difficult to establish the half-life of antibody in patients with widely degrees of tumor burden receiving a single nonsaturating dose of antibody" and reports that in the study at hand, "[l]ower levels [of antibody] were identified in patients with extensive disease." Ex. 1003, 9. Those patients were LG-NHL patients, not CLL patients, as discussed above.

Petitioner relies on Dr. Ozer to reach the conclusion that "patients with more extensive disease" refers to CLL patients. But instead of addressing what "patients with more extensive disease" refers to in Maloney 1994, Dr. Ozer subtly introduces an entirely new concept found nowhere in Maloney 1994—the concept of "patients with **a** 'more extensive disease.'" Ex. 1002, ¶ 55. Dr. Ozer's addition of the indefinite article "a" here suggests that there existed a hierarchy of different diseases, with some diseases considered more "extensive" than others. Dr. Ozer does not establish that any such hierarchy actually existed in the art. And nothing in Maloney 1994 implies one. Referring to Maloney 1994, Dr. Ozer states that "CLL is the only such 'more extensive

disease' mentioned in the article." *Id*. But Maloney 1994 nowhere characterizes any disease, let alone CLL in particular, as "more extensive" than any other disease; Dr. Ozer's statement is completely unfounded.

Petitioner asserts that CLL patients were known to have "generally had much higher tumor burdens" than LG-NHL patients. Ex. 1002, ¶ 55; Pet. 32. But that is not evidence that a POSA would have considered CLL to be a "more extensive disease" or that Maloney 1994 was describing CLL patients when it referred to "patients with more extensive disease."

Any doubt regarding which patients Maloney 1994 was referring to when it suggested that "[e]xtension of these studies using multiple doses to achieve prolonged, tumor-saturating levels may lead to responses in patients with more extensive disease" would have been removed by Maloney's own extension of those studies, as reported in Maloney (Sept.) 1997. Those extension studies used multiple rituximab doses to achieve prolonged, tumor-saturating levels in LG-NHL patients and reported that this led to responses in such patients with "bulky" disease, just as Maloney 1994 suggested. Ex. 1004, 6. Not only did the extension studies target NHL patients—not CLL patients—they specifically *excluded* CLL patients. *Id*. ("[P]atients with chronic lymphocytic leukemia (CLL) were excluded from this trial (based on the presence of >5,000 lymphocytes/μL for this histological subtype)[.]").

Accordingly, a POSA would not have interpreted Maloney 1994 as having suggested that rituximab should be used to treat CLL patients.

Indeed, the exclusion of CLL patients from these extension studies would have discouraged a POSA from trying to use rituximab to treat CLL patients. The results would have too. They showed that patients with SLL did not respond to treatment with rituximab, whereas patients with other NHL histologies did respond. Ex. 1004, 6. The authors posited that the lack of response in SLL patients may have been "due to a lower expression of the CD20 surface antigen," as had "been observed in cases of CLL." *Id*.

C. Petitioner Fails To Establish Any Reasonable Expectation Of Success.

Petitioner relies on "the Genentech Press Release" as its purported evidence of a reasonable expectation of success. Pet. 33-34. According to Petitioner, "[t]he Genentech Press Release [would have] provided a POSA with a reasonable expectation of success in using rituximab to treat CLL." Pet. 33. It would have done no such thing. But even assuming otherwise, Petitioner's argument fails on multiple grounds.

1. Petitioner Did Not Show That "The Genentech Press Release" Would Have Provided A POSA With A Reasonable Expectation Of Success In Using Rituximab To Treat CLL.

Petitioner contends that "the Genentech Press Release" disclosed "that Patent Owners were conducting rituximab clinical trials with CLL patients,"

and that this, "alone, would have provided a POSA with a reasonable expectation of success in using rituximab to effectively treat CLL." Pet. 33-34.

(a) Petitioner Never Demonstrated That "The Genentech Press Release" Is A Prior Art Printed Publication.

As discussed in Section IV above, Petitioner failed to establish that Ex. 1006 ("The Genentech Press Release") is a prior art printed publication on which *inter partes* review can be based. Accordingly, Petitioner cannot rely on "the Genentech Press Release" to establish that a POSA would have had a reasonable expectation of success at the time of the invention.

(b) "The Genentech Press Release" Does Not Disclose That Any Trial Of Rituximab In CLL Was Being Conducted.

Contrary to Petitioner's assertion, "the Genentech Press Release" does not contain a "disclosure that Patent Owners were conducting rituximab clinical trials with CLL patients." *Id*. Rather the "Press Release" simply says that Genentech and Idec were "planning" certain additional studies, including studies "in other B-Cell mediated cancers such as intermediate grade NHL and chronic lymphocytic leukemia." Ex. 1006, 1. No details regarding any such plans are disclosed in the document.

Petitioner also asserts that the "Press Release" document "disclosed Patent Owners' encouraging research involving the use of rituximab to treat CLL patients." Pet. 14. But again, the document contains no such disclosure.

Indeed, because any studies of rituximab in CLL were, at most, merely being planned, there did not exist any such CLL research—encouraging or otherwise—to be disclosed. The only "encouraging results" described by the "Press Release" were from a phase II study of rituximab in NHL, which led to a scheduled phase III trial in NHL to "attempt to confirm these results." Ex. 1006, 1. Nowhere does the "Press Release" link these "encouraging results" in NHL patients to potential plans for trials in CLL patients, contrary to Petitioner's assertion that the "Press Release" "disclosed that they [Patent Owners] were 'planning' clinical trials with rituximab to treat patients with 'chronic lymphocytic leukemia' ***based on*** 'encouraging results' using the drug for another cancer." Pet. 2 (emphasis added).

Selectively quoting "the Genentech Press Release," Petitioner argues that studies were being planned "'***to support' treatment*** of 'B-cell mediated cancers such as . . . *chronic lymphocytic leukemia.*" Pet. 33 (ellipses in original). "The Genentech Press Release" refers only once to studies to support treatment, however, and when it does, it refers to studies "to support [a] primary indication in NHL," not studies to support treatment of CLL. Ex. 1006, 1. Petitioner omits "this primary indication in NHL" from its quotes to manufacture support for its misguided position.

(c) Even If "The Genentech Press Release" Disclosed That A Trial Of Rituximab In CLL Patients Was Being Conducted, The Mere Initiation Of A Clinical Trial Would Not Have Established A Reasonable Expectation Of Success.

Petitioner would have failed to establish a reasonable expectation of success even if "the Genentech Press Release" disclosed that a trial of rituximab in CLL patients was being conducted. It is also well known, for example, that clinical trials are, in fact, routinely unsuccessful. *See* Ex. 2010, 009 (showing that oncology trials are the least likely of all to be successful).

Petitioner tries to rely on authority grounded in Section 101's utility requirement to argue that the initiation of human clinical trials can establish a reasonable expectation of success in the context of Section 103. *See* Pet. 33-34. Specifically, Petitioner relies on MPEP § 2107.03.IV, which describes minimum thresholds for establishing "therapeutic utility" to satisfy the ***utility*** requirement of Section 101 during patent prosecution. Petitioner cites no authority suggesting that any of these thresholds also apply to the "reasonable expectation of success" requirement under Section 103.

Petitioners contend that "'studies are frequently conducted to confirm what is suspected to be true.'" Pet. 34. But nothing in "the Genentech Press Release" suggests that a clinical trial of rituximab in CLL patients would serve as a "confirmatory study" that would "confirm what is suspected to be true."

Pet. 34 (citing *Soft Gel Techs., Inc. v. Jarrow Formulas, Inc.*, 864 F.3d 1334, 1342 (Fed. Cir. 2017). Nor does the "Press Release" describe the methodology that would underlie any such "confirmatory study." Indeed, the "Press Release" does not even mention a proposed dosage, nor does it suggest any of the clinical endpoints that a POSA would have identified for successful treatment if all that was really left to do was to "confirm what [was] suspected to be true." *Soft-Gel Techs., Inc.*, 864 F.3d at 1342.

Petitioner further cites *Biomarin Pharm. Inc. v. Genzyme Therapeutic Products Ltd.*, No. IPR2013-0534, Paper No. 81, at 17 (P.T.A.B. Feb. 23, 2015) in support of its argument that it would have taken only "routine" work to "verify the expectation that a specific dosage (within a previously suggested dosage range) and corresponding dosage regimen would have been safe and effective." Pet. 34 (citing *Biomarin*, at 17). But unlike in *Biomarin*, here there is no "absence in the record of evidence identifying a difference between the prior art and the subject matter of the claims." *Id.* at 18. Indeed, the record documents many such differences. *See* § V.B.1. Moreover, the art also fails to give any guidance as to diagnosis, dosage, number of doses, clinical endpoints, or many other parameters that a POSA would have considered if one ever would have planned to treat CLL patients with an experimental therapy like rituximab. This is particularly true given that antibody therapeutics had not previously been tested in CLL by the time of the

alleged "Press Release." *See*, *e.g.*, Ex. 1009, 1 (reporting that as of 1998, treatment of CLL with rituximab "has not been investigated yet"); Ex. 1008, 33-36.

2. Petitioner Never Even Attempted To Prove Reasonable Expectation Of Success Under The Correct Construction Of "amount effective to treat the chronic lymphocytic leukemia."

Petitioner argues only that a POSA would have had a reasonable expectation of success in "effectively treating the CLL by achieving a reduction in circulating, CD20-positive tumor cells." Pet. 45.

As discussed in § III.B, however, the claims require more than just depletion of circulating tumor cells (*i.e.* B cell depletion)—they require a positive clinical benefit. A positive clinical benefit also requires addressing the patient's outward symptoms (such as fatigue and fever), the size of the patient's lymph nodes and spleen/liver, and the patient's blood count (red blood cells and platelets). *See id*. Petitioner fails to establish that reducing circulating CLL tumor cells would have been sufficient to provide a POSA with a reasonable expectation of a clinical benefit. *See* § III.B.1.

Petitioner has not alleged, let alone shown, that a POSA would have achieved, or expected to achieve, any such benefit by following the teachings of the Maloney references. Moreover, Petitioner's evidence suggests that even if a POSA would have expected rituximab to deplete B cells in CLL, a POSA

would not have expected rituximab to deplete B cells to a sufficient degree to achieve the required positive clinical benefit. The successful B-cell depletion in NHL patients in Maloney 1994 involved patients who had approximately 1% of the total number of tumor cells as compared to a CLL patient. *See* Pet. 42; Ex. 1003, 7 (Table 3). In the patients with the highest tumor burdens (Patient Nos. 001 and 002), B-cell depletion was not as complete as the patients with lower initial tumor burdens (*e.g*. Patient Nos. 013-015). Petitioner has not explained how or why a POSA would extrapolate these results to assume that sufficient B-cell depletion would occur by administering rituximab to patients with 100-fold greater tumor burdens and lower CD20 densities, such as CLL patients.

These significant and unexplained hurdles that a POSA would have needed to overcome to treat CLL with rituximab preclude any reasonable expectation of success, particularly in light of the Federal Circuit's holdings that the field of biotechnology is "unpredictable" and that "potential solutions are less likely to be genuinely predictable." *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

D. Petitioner Fails To Establish That The Claimed Dosages Were Obvious.

Petitioner contends that the prior art rendered doses of 375 mg/m^2 and 500 mg/m^2 obvious, and that each of claims 2-7 is rendered obvious if those

doses are obvious. Pet. 36. Specifically, Petitioner argues that (a) the 375 and 500 mg/m^2 doses are presumed *prima facie* obvious in view of Maloney 1994; (b) the 375 and 500 mg/m^2 dose would have been obvious in view of Maloney 1994 and Maloney (Sept.) 1997; and (c) that a POSA would have arrived at the claimed dosages by routine optimization. None of these arguments has merit.

1. Petitioner Has Not Demonstrated that the Claimed Dosages Are Presumed *Prima Facie* Obvious In View Of Maloney 1994.

Citing *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317 (Fed. Cir. 2004), Petitioner argues that doses of 375 mg/m^2 and 500 mg/m^2 are "presumed to be *prima facie* obvious" because they "were within the range of doses disclosed by the Maloney 1994 reference." Pet. 37-38. But unlike the prior art references in *Iron Grip Barbell*, Maloney 1994 does not disclose *all claim elements except* for a specific numerical value within a disclosed range. As explained above, Maloney 1994 discloses treating LG-NHL, not CLL. It does not even suggest treating CLL with rituximab, let alone disclose a range of doses for treating CLL with rituximab. Thus, this is not a case where "a range [is] disclosed in the prior art, and the claimed invention falls within that range." *Iron Grip Barbell*, 392 F.3d at 1322. The claims here are not presumed obvious under *Iron Grip Barbell.*

Petitioner tries to recast the analysis by arguing that "[a]ny dose within [the range disclosed in Maloney for LG-NHL] is presumed *prima facie* obvious

when used to achieve the ***same effect*** of depleting B cells." Pet. 38 (emphasis added). But the claims do not require an amount of rituximab for "depleting B cells." They require "an amount effective to treat the chronic lymphocytic leukemia," which means providing a positive clinical benefit to the CLL patient. *See* § III.A. Maloney 1994 makes no suggestion to treat CLL patients with rituximab, at 375 mg/m^2, 500 mg/m^2, or at any other dose. It doesn't even suggest that rituximab would successfully bind CD20 on the B-cells in CLL patients, as the only mention of CLL in the article draws an express contrast between CD20's expression in B-cell NHLs as compared to CLL. *See* § V.C.1(c). Accordingly, Petitioner has failed to establish that the claimed 500 mg/m^2 rituximab dose for CLL was *prima facie* obvious under *Iron Grip Barbell.*

2. Petitioner Has Not Demonstrated That Doses Of 375 mg/m^2 or 500 mg/m^2 Would Have Been Obvious In View Of Maloney 1994 In View Of Maloney (Sept.) 1997.

As an alternative theory, Petitioner contends that "it would have been most obvious to use the claimed 500 mg/m^2 dose when treating CLL patients, and also obvious to use—or at least start therapy with—lower initial doses (e.g., 375 mg/m^2) in the event of infusion related toxicities." Pet. 38. Patent owner addresses each of these arguments in turn.

(a) The 500 mg/m^2 Dose Was Not "most obvious."

Focusing on Maloney 1994 and Maloney 1997, Petitioner contends that "[t]he teachings from these two references, when combined with the knowledge of a POSA that CLL patients had approximately 100 times more tumor cells than NHL patients, suggested that a high rituximab dose likely would be needed to treat CLL." Pet. 38. But one of the "teachings" Petitioner relies on is the disclosure of a "dose-dependent, rapid and specific depletion of B cells" in Maloney's NHL patients. Pet. 37. Indeed, Dr. Ozer concludes that "'a POSA would have appreciated that the total amount of rituximab needed to bind to tumors is proportional to the total number of tumors that need to be destroyed.'" Ex. 1002, ¶ 76 (quoting a statement by Patent Owners in a different IPR proceeding in the context of NHL).

Petitioner assumes that a POSA would have considered this dose-dependent depletion of B cells in NHL patients to be predictive of B-cell depletion in CLL patients. Pet. 42. Petitioner never justifies this assumption, and the record calls it into question. For example, as Dr. Ozer observes, "the lower density of CD20 [in CLL patients] meant that rituximab would have smaller targets to bind to, and thus a lower probability of successfully binding to the target than in B-cells with higher CD20 densities," like those in the NHL patients discussed in Maloney 1994. Ex. 1002 at ¶ 49. Dr. Ozer's statements confirm that the art recognized a difference in antibody-antigen binding

kinetics in NHL and CLL. This suggests that a POSA would not have just taken Maloney's findings regarding dose-dependent B-cell depletion in NHL and blindly extrapolated them to the treatment of CLL, where a POSA would have anticipated a lower binding success.

Petitioner's argument fails even assuming that a POSA would have believed that the total amount of rituximab needed to bind to tumors in CLL patients is proportional to the total number of tumors that need to be destroyed. Petitioner claims that this, "when combined with the knowledge of a POSA that CLL patients had approximately 100 times more tumor cells than NHL patients, suggested that a high rituximab dose likely would be needed to treat CLL." Pet. 38. But this rationale would have led a POSA to try in CLL patients doses of rituximab much higher than the doses up to 500 mg/m^2 that Maloney suggests for NHL patients, assuming a POSA would have been motivated to try rituximab to treat CLL in the first place. If a POSA would have believed that the dose of rituximab needed for CLL patients is proportional to the number of tumors cells, then knowledge that CLL patients have approximately 100 times more tumor cells than NHL patients would have prompted a POSA to use a dose of rituximab for CLL patients that is approximately 100 times higher than the dose of rituximab for NHL patients. Petitioner contends that Maloney (Sept.) 1997 "disclosed using 375 mg/m^2 of rituximab in each of four

weekly doses as the preferred regimen for NHL patients."[5] Pet. 45-46. According to Petitioner's logic, therefore, a POSA would have used 37,500 mg/m^2 doses of rituximab in CLL patients.

Petitioner contends that a POSA would have found a dose of 500 mg/m^2 "most obvious." But Petitioner cites nothing in the prior art suggesting that a 100-fold increase in tumor cells having a six fold lower density of CD20 relative to NHL could be accounted for by a mere 33% increase in the dose of rituximab relative to "the preferred" NHL dose of 375 mg/m^2.

Petitioner argues that a POSA would have found the 500 mg/m^2 dose "most obvious" because it is the "only dose above 375 mg/m^2" disclosed by the Maloney references. Pet. 46. But this relies on the false premise that "Maloney (Sept.) 1997 taught that 375 mg/m^2 was the dose of choice for treating NHL patients." Pet. 38. In fact, Maloney (Sept.) 1997 nowhere states that 375 mg/m^2 is the preferred or ideal dose for NHL; it simply identifies 375 mg/m^2 as the dose the authors elected to use for their phase II trial. *See* Ex. 1004, 2. The article studied only 37 patients, and proposes further investigation of rituximab in NHL to explore "extended and repeated dosing regimens" in NHL. *Id*. at 7. Accordingly, Maloney did not reach any conclusions regarding the "dose of

[5] Maloney (Sept.) 1997 does not actually disclose 375 mg/m^2 as the preferred dose, as discussed further below.

choice for NHL." Nor did Maloney 1994 teach or suggest any theoretical maximum dose of rituximab. To the contrary, Maloney reported that "no dose-limiting toxicities were identified," even at the highest dose level. Ex. 1003, 9.

Moreover, as noted above in Section III.A, Jensen suggested that in CLL patients, a 375 mg/m^2 dose for rituximab "might be too high." Ex. 1009, 2. Thus, prior art available at the time of filing suggested that even a dose "lower" than 500 mg/m^2—375 mg/m^2—may be too high to be safe, negating any suggestion to use an even higher dose with any expectation of success.

(b) The 375 mg/m^2 Dose Was Not An Obvious Dose For Preventing Infusion-Related Toxicity.

Petitioner also argues that a 375 mg/m^2 dose would have been obvious because "lower initial doses may be necessary to offset infusion-related toxicity" before increasing the dose to 500 mg/m^2. Pet. 39. The argument fails at least because of its reliance on the erroneous conclusion that the 500 mg/m^2 dose was "most obvious." *See* § V.D.2(a).

The argument also fails because Petitioner cites inapposite evidence from Maloney 1994 regarding infusion ***rates*** as allegedly rendering the 375 mg/m^2 dose obvious. Pet. 39 (describing Maloney 1994, Ex. 1003 at 6, varying infusion rate from "50 to 100 mg [per hour] and then escalat[ing the infusion rate] as tolerated to 200 mg [per hour,]" when side effects were

observed). But a discussion of rituximab infusion rate (*i.e.* how fast) would not at all have informed which dose of rituximab (*i.e.* how much) a POSA would have administered. The different units used to describe each parameter highlight the irrelevance of Petitioner's cited evidence: infusion rate is measured in milligrams per hour (mg/h) whereas dosage is measured in milligrams per meter squared (mg/m^2). *See* Ex. 1006, 6.

Petitioner also contends that concern over tumor lysis syndrome ("TLS") "would have suggested to a POSA to start with a lower initial dose of rituximab," Pet. 39, n. 10, and that POSAs would have selected 375 mg/m^2 as such a dose. *Id.* at 39-40. Petitioner points to its discussion of TLS at § IX.D.1.b of its petition (pages 57-62) as support. But in that section, Petitioner cites Jensen's disclosure that "[t]he recommended standard dose of 375 mg/m^2 for rituximab . . . ***might be too high*** for the patients with substantial peripheral tumor load." Pet. 59. In the next sentence, Petitioner states that "a POSA would construe this teaching as urging caution before starting a CLL patient with a ***relatively high*** rituximab dose until tolerability is confirmed. At that point, the dose could be increased—e.g., to 375 mg $m/^2$ or 500 mg/m^2." *Id*.

Petitioner cannot have it both ways. In discussing the full disclosures of the prior art in § IX.D.1.b of the petition, including its characterization of 375 mg/m^2 as a "relatively high rituximab dose," Petitioner reveals that its argument is driven by hindsight. There is simply no suggestion in the art that a

POSA would have selected a 375 mg/m^2 dose as a low initial dose to protect against infusion-related side effects. In fact, the art and Petitioner's own admissions suggest just the opposite. This contradiction is fatal to Petitioner's argument. *See Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 921 (Fed. Cir. 2011) ("[I]t is impermissible to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.").

(c) Petitioner Cannot Reach The Claimed Doses By So-Called Optimization.

Petitioner asserts that a POSA would have arrived at the claimed dosages by routine optimization, Pet. 42, but fails to make the required showing.

First, the result of the "optimization" process must in fact be an "optimum value" for the variable. *In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977); *In re Aller*, 220 F.2d 454, 458 (C.C.P.A. 1955) ("No invention is involved in discovering *optimum* ranges of a process by routine experimentation.") (emphasis added). Petitioner never even asserts, much less submits evidence demonstrating, that the either of the 375 mg/m^2 or 500 mg/m^2 doses was, in fact, "an optimum."

Second, the variable being optimized must have been "*known*" to be "*result-effective*." *In re Antonie*, 559 F.2d at 620 (rejecting a routine

optimization argument because "the parameter optimized was not recognized to be a result-effective variable") (emphasis added). Petitioner does not establish that rituximab dosing was considered "result effective" in CLL. Maloney's finding of dose-dependence in NHL, does not speak to rituximab's dose-response relationship in CLL, which is a distinct histology as compared to NHL. This fact is recognized by Petitioner itself when it contends that CLL B-cells would react differently to rituximab treatment as compared to LG-NHL B-cells at least because of "the lower density of CD20 on CLL B-cells"—a difference "akin to having a smaller 'target' for rituximab to hit, making it less likely that any given unit of rituximab successfully binds to the CD20 antigen." Pet. 39. This is an admission by Petitioner that rituximab's binding and kinetics in LG-NHL would have been understood by a POSA to be different from those in CLL.

Accordingly, varying the rituximab dose was not known be "result-effective." *See id.*; *In re Yates,* 663 F.2d 1054, 1056 (C.C.P.A. 1981) (rejecting a routine optimization argument because the allegedly optimized parameter "was not recognized to be a result-effective variable"); *cf. In re Urbanksi*, 809 F.3d 1237, 1242 (Fed. Cir. 2016), ("[R]eaction time and degree of hydrolysis are result-effective variables that can be varied in order to adjust the properties of the hydrolyzed fiber *in a predictable manner*.") (emphasis added).

Third, the evidence must show that the experimentation needed to optimize the variable also was known in the art. *In re Fay*, 347 F.2d 597, 602 (C.C.P.A. 1965) ("To support the board's decision that 'routine experimentation within the teachings of the art' will defeat patentability requires a primary determination of whether or not appellants' experimentation comes *within the teachings of the art*."). Petitioner fails to provide any evidence describing the experimentation process that allegedly would have been needed to arrive at the claimed doses, much less evidence that such experimentation was known in the art. Indeed, Petitioner does not even suggest any experimentation that a POSA would have undertaken; Petitioner merely suggests that a POSA would have tried a dose of 375 mg/m^2 because it was purportedly the dose of choice in NHL (as explained above, it was not), and would have selected the claimed 500 mg/m^2 dose because it was "[t]he only dose above 375 mg/m^2 disclosed as safe and effective in Maloney 1994." Pet. 38. But Maloney 1994 only addressed LG-NHL patients, and never suggested that doses above 500 mg/m^2 would not be safe and effective. To the contrary, Maloney reported that "no dose-limiting toxicities were identified," even at the highest dose level. Ex. 1003, 9.

Fourth, the prior art must "have suggested to one of ordinary skill in the art that this [experimentation] process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art." *Merck &*

Co. v. Biocraft Labs., Inc., 874 F.2d 804, 809 (Fed. Cir. 1989) (quotation marks omitted). The evidence adduced by Petitioner suggests precisely the opposite. As discussed above, if a POSA would have believed that the dose of rituximab needed for CLL patients is proportional to the number of tumors cells, and if CLL patients have approximately 100 times more tumor cells than NHL patients, then a POSA seeking to "optimize" the dose of rituximab for CLL patients would have expected that a dose much higher than the 375 mg/m^2 or 500 mg/m^2 doses upon which Petitioner relies would be needed to treat CLL patients. *See* § V.D.2(a).

Fifth, the experimentation required to arrive at the claimed optimum must, as the label "routine optimization" implies, be no more than routine. *Id.* ("The evidence at trial showed that, though requiring time and care, the experimentation needed to arrive at the claimed dosages was nothing more than routine."). Petitioner fails to submit evidence establishing that any experimentation here would have been merely routine. Even assuming that rituximab was known at the time to be effective in CLL (it was not), in light of the relationship between required dose and number of circulating cells suggested by Petitioner, and the different densities of CD20 on CLL cells versus LG-NHL cells, the experimentation required to determine the optimum rituximab dose for CLL patients would have been far from routine. Petitioner's methodology suggests the need for extraordinarily high doses in comparison to

what was known, which would require extensive experimentation to balance efficacy, infusion safety, and toxicity. Petitioner has not even described the process a POSA allegedly would have followed; it jumps straight to the claimed dosages based on hindsight.

3. More Than Just "A Reasonable Expectation Of Success In Using Rituximab To Treat CLL" Is Required In Any Event To Satisfy Claims 2-7.

Even assuming "the Genentech Press Release" would have provided a "POSA with a reasonable expectation of success in using rituximab to treat CLL," as Petitioner contends, Pet. 33, the reasonable expectation of success requirement still would not be met because Petitioner would have to further show an expectation of success in using the claimed dosages to treat CLL. "The Genentech Press Release" is silent as to any dosing for CLL. And the record suggests that a POSA would have expected the claimed dosages to be too low to treat CLL, as discussed above. *See* § V.D.2.

E. The Claimed Invention Was Not Obvious To Try.

Petitioner also tries to rectify its failure to identify in the prior art any disclosure of using rituximab to treat CLL at any dose by contending that the use of rituximab to treat CLL and the use of the claimed doses of rituximab were "obvious to try." In serial conclusory assertions, Petitioner contends first that rituximab was "one of a finite number of identified, predictable solutions for treating B-cell cancers such as CLL," Pet. 36, and later that the claimed

doses "fall within a finite number of identified, predictable dosing solutions for treating CLL with rituximab." Pet. 42 (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)).

These contentions fail because they misapply the legal standard: the "question is whether ***the invention*** is an 'identified, predictable solution' and an 'anticipated success,'" and not whether a narrowly defined claim element, like the claimed dosages, can be plucked out of an artificially narrow cross-section of the prior art. *Rolls-Royce, PLC v. United Techs. Corp.*, 603 F.3d 1325, 1339 (Fed. Cir. 2010) (emphasis added). Notwithstanding Petitioner's failure to meet this threshold requirement, its reliance on this rationale fails in several additional respects.

Petitioner has not established that the alleged problems it identified were "problem[s] known in the art." *Purdue Pharma L.P. v. Depomed, Inc.*, 643 Fed. App'x 960, 966 (Fed. Cir. 2016) (citing *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015)). As explained above, § V.B, Petitioner has not identified in the art (which discussed NHL) any disclosures of using rituximab to treat CLL, let alone disclosures that "optimiz[ing] the rituximab dose to treat CLL" was a known problem. Every time Petitioner relies on this rationale, *see* Pet. 36, 42. 48. 51, and 52, Petitioner simply "[d]efine[s] the problem in terms of its solution," by asserting that the specific ***claim element*** at issue was a problem known in the art. *Purdue Pharma*.,

643 Fed. App'x at 966. This "reveals improper hindsight in the selection of the prior art relevant to obviousness." *Id*. Such an approach cannot cure Petitioner's failure to identify any purported "known problem" in the prior art.

Moreover, Petitioner has not "point[ed] to any evidence in the record or reasoning suggesting that the possible approaches" to solving either alleged problem were actually "known and finite." *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, No. IPR2017-01585, Paper No. 8, at 19 (P.T.A.B. Dec. 15, 2017). Alleging that a particular claim element is drawn from one of a "finite number of predictable solutions" without "sufficient evidence or explanation" that the solution was somehow limited" amounts to "a hindsight statement based on the invention described in the ['612] patent," and not based on what was known in the art. *Id.* at 19-20.

The cited portions of Dr. Ozer's declaration illustrate that Petitioner simply ignores the numerous, standard of care treatment regimens known in the art for treating CLL, illustrated at least by the cited pages of Kipps. Ex. 1008, 23, 34-36. For example, Kipps discloses the treatment of CLL with: numerous classes of chemotherapy, including: glucocorticoids, alkylating agents, fludarabine, cladribine, pentostatin, and cytosine arabinoside—each at varying potential dosages; combination chemotherapy using the aforementioned classes of agents at unspecified dosage ranges; splenectomy; radiation therapy; leukaphareses; marrow or blood stem cell transplantation;

and immunotherapy and biologic response modifiers. *Id.* at 34-36. Neither rituximab (nor any synonym) is mentioned at all amongst these numerous approaches. Thus, "the broad selection of choices for further investigation available to a person of ordinary skill" included near limitless possibilities, and indeed, as explained above, "the record does not show that one of ordinary skill in the art would have any reason to try [rituximab in CLL] at all," let alone at the claimed dose. *Rolls-Royce, PLC.*, 603 F.3d at 1339 (Fed. Cir. 2010).

In any event, "[f]or an invention to be obvious to try, there must be a finite number of known choices in the prior art, **and** a reasonable expectation of success for the choice that is tried." *See Hoffmann-La Roche Inc. v. Apotex, Inc.,* 748 F.3d 1326, 1340 (Fed. Cir. 2014) (emphasis added). Petitioner fails to establish a reasonable expectation of success.

F. The Administration Limitations In Claims 16-20 Would Not Have Been Obvious.

Claims 16-20, which depend from claim 1 or claim 6, would not have been obvious for all of the reasons that claims 1 and 6 would not have been obvious. *See* Sections V.A-E.

Even if the studies of Maloney 1994 and Maloney (Sept.) 1997 had been conducted in CLL patients, instead of NHL patients, Petitioner still would not have established that dependent claims 19-20—which require bi-weekly and monthly administration of rituximab, respectively—would have been obvious.

Maloney 1994 discloses administering only a single dose of rituximab to each patient, and Maloney (Sept.) 1997 discloses only weekly dosing (with none of the weekly doses in the amount of 500 mg/m^2, as claimed).

Petitioner argues that Maloney 1994 "taught that single doses between 50 mg/m^2 to 500 mg/m^2 depleted CD20-positive B-cells for between one and three months in NHL patients" and "thus taught a POSA that rituximab, when administered in a dose within this range, should be administered at least once a month." Pet. 45. But that assumes that a POSA would have administered rituximab with the goal of maintaining depletion of all B cells in patients, as opposed to, for example, trying to deplete cancerous B cells once and for all and then allowing healthy B cells to grow back. Petitioner cites no evidence that a POSA would have sought to maintain depletion of all B cells in CLL patients. Maloney (Sept.) 1997 suggests that maintaining depletion of all B cells was not even the goal in treating NHL patients, given that Maloney administered rituximab to those NHL patients in four weekly doses of 375 mg/m^2, completing administration within the window of depletion that Petitioner contends would have been expected from the first dose. Accordingly, separate and apart from Petitioner's failure to establish that independent claims 1 and 6 would have been obvious, Petitioner also failed to establish that dependent claims 19 and 20, with their bi-weekly and monthly dosing requirements, would have been obvious.

VI. GROUND II: THE COMBINATION OF THE MALONEY REFERENCES AND THE PRESS RELEASE DOES NOT RENDER CLAIMS 23-35, 37-45, OR 59 OBVIOUS

Petitioner argues that claims 23-35 and 37-44 "are identical to the preceding claims, but include the limitation 'wherein the anti-CD20 antibody therapy is combined with chemotherapy." Pet. 49. Thus, this ground fails for all the same reasons that Ground I fails. *See* § V. Moreover, as explained in further detail below, it would not have been obvious to combine rituximab and chemotherapy to treat CLL patients.

A. The Ground Fails For All The Reasons Ground I Fails.

Ground II fails for all the same reasons that Ground I fails, including because Petitioner failed to establish that the "Genentech Press Release" is a prior art printed publication. *See supra* Section V. The addition of Maloney (Oct.) 1997 to this ground does not cure the deficiencies in Ground I, as explained below.

B. None Of The References Relied Upon In This Ground Discloses The Treatment Of CLL With Chemotherapy.

Petitioner does not even allege that any reference cited in this ground disclosed the treatment of CLL with chemotherapy. Instead, Petitioner interprets Maloney (Sept.) 1997's disclosure of potential future research projects to suit its arguments by suggesting that Maloney urged a POSA to explore the use of combination therapy in CLL. *See* Pet. 50. Because Maloney

(Sept.) 1997 never mentions CLL by name, Petitioner latches onto its proposal for "evaluation [of rituximab] in other B-cell histologies," as allegedly suggesting its use in CLL. Pet. 50 (citing Ex. 1004, 7). At best, the disclosure of "other B-cell histologies," amounts to "a laundry-list of untested potential targets[, and] would [not] have provided sufficient direction to one of ordinary skill in the art to select [CLL]." *See Amgen, Inc. v. Abbvie Biotechnology, Inc.*, No. IPR2015-01514, Paper No. 9, at 18 (P.T.A.B. Jan. 14, 2015).

Moreover, even if the disclosure of "other B-cell histologies" could be interpreted as suggesting the use of rituximab in CLL (it cannot), the structure and punctuation of the sentence show that at most, Maloney (Sept.) 1997 suggested the evaluation of rituximab *monotherapy* in other, unspecified, B-cell histologies. *See* Ex. 1004, 7 ("Additional areas that should be investigated using this new agent include (1) extended and repeated dosing regimens, (2) combination with or after standard chemotherapy, (3) use as an in vivo B-cell purging agent before collection of bone marrow or stem cells for high-dose therapies, (4) evaluation in other B-cell histologies, and (5) lymphomas arising in association with immune-deficiency such as acquired immunodeficiency syndrome or organ transplantation."). The numerical subheadings for each proposed area of investigation show that Maloney did not suggest trying each of the enumerated suggestions in combination. Indeed, a POSA would not have been motivated to combine rituximab with

chemotherapy in "other B-cell histologies," before first testing rituximab monotherapy in such histologies, none of which are specified. To do otherwise would be contrary to norms of medical testing and the scientific method.

C. A POSA Would Not Have Combined Rituximab With Chemotherapy In CLL Patients.

Petitioner contends that "[t]he two Maloney References from 1997 also made it obvious to use rituximab with chemotherapy to treat CLL patients." Pet. 50. Contrary to Petitioner's assertion, and as established above, the Maloney references disclose nothing regarding the treatment of CLL, and in fact suggested that rituximab may be ineffective in binding the CD20 antigen as it presents on B-cells in CLL patients.

1. Rituximab's Purported Ability To Chemosensitize B-Cells Would Not Have Solved The "Targeting" Problem Petitioner Identified With Respect To Rituximab Monotherapy.

Petitioner contends that Maloney (Oct.) 1997 suggested a rationale for combining rituximab and chemotherapy because it reported that rituximab may, "in some resistant human ***lymphoma*** cell lines," Ex. 1005, 4, "make[]

tumor cells more vulnerable to chemotherapy." Pet. 50.[6] This rationale is unavailing for several reasons.

First, as explained in § V.D.3, Maloney's experience using rituximab in NHL patients suggested that it would not work the same in CLL. Contrary to Dr. Ozer's assertion that "the same CD20-expressing B-cells in NHL patients are present in CLL patients," Ex. 1002, ¶ 99, the art established otherwise, and indeed Dr. Ozer himself repeatedly contradicts this. See §§ II.A; V.D.3. Petitioner's entire rationale for (i) using a 500 mg/m^2 rituximab dose in CLL patients; and (ii) adding chemotherapy to such a regimen, is premised on the fact that B-cells in CLL patients are more numerous and express the CD20 antigen differently, thus requiring more intensive treatment. *See*, *e.g.*, Pet. 49 (Suggesting "add[ing] chemotherapy treatment because of the higher tumor burdens and lower CD20 expression, which made it potentially harder for rituximab to completely treat CLL on its own.").

[6] Maloney cites Demidem 1997, Ex. 1032, for this proposition. Demidem studies the effects of rituximab on the "DHL-4 B lymphoma cell [line] to various cytotoxic drugs/toxins." *Id*. at 6. The only cytotoxic agents studied are Diptheria Toxin (DTX), Cisplatin Diammine Dicholoride (CDDP), Adriamycin (ADR), etoposide, and TNF-α, and ricin. *See*, *e.g.*, *id.*at 7 (Table 2).

Moreover, the cited section of Dr. Ozer's declaration demonstrates that Petitioner is confused. Dr. Ozer states that "the higher tumor burden of CLL patients and the lower CD20 expression would make it harder to treat CLL with rituximab alone." Ex. 1002 at ¶ 101. He then states that "Maloney (Oct.) 1997 taught that rituximab 'increases sensitivity to the cytotoxic effect of chemotherapy/toxins in some resistant human lymphoma cell lines,' which means that rituximab makes tumor cells more vulnerable to chemotherapy." *Id*. Petitioner has it backwards.

As Petitioner recognizes, "the higher tumor burdens and lower CD20 expression" in CLL patients would have made it "harder for rituximab to completely treat CLL on its own." Pet. 50. Even if rituximab was able to increase the sensitivity of B-cells in CLL patients to chemotherapy (which Petitioner has not established), at best, under Petitioner's theory, this would sensitize only those B-cells to which the rituximab was able to bind. This does not solve the problem that Petitioner identified with respect to using rituximab in CLL—namely, that it is less likely for rituximab to "hit" the CD20 target. Pet. 39.

Following Petitioner's logic, as compared to NHL, a lower proportion of B-cells in a CLL patient would be "hit" by rituximab, and thus a relatively small portion of those cells would be sensitized to chemotherapy. Even if that sensitization were to occur, it would not have suggested to a POSA that such a

combination would help reduce the 100-fold greater tumor burden present in CLL patients.

2. Petitioner Has Not Proven That Either Rituximab Or Chemotherapy Were Able To Attack CLL Using Different Mechanisms Of Action.

Petitioner also contends that it would have been "obvious to try combination therapy," because "[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." Pet. 51. As explained above, Petitioner has not cited a single instance in which a POSA targeted CLL with either rituximab or chemotherapy. As the Board found in rejecting this rationale in IPR2017-01167:

> [T]o the extent that Petitioner asserts that it would have been obvious to combine rituximab with [chemotherapy] because of their separate mechanisms of action, we remain unpersuaded. . . . In support of that assertion, Petitioner refers to *Novo Nordisk* , 719 F.3d at 1351. However, in *Novo Nordisk*, the principle upon which Petitioner relies involves a situation wherein two drugs have different mechanisms of treating the *same disease*. *Id*. (obvious to try combination therapy when it was "well-known in the art that two drugs having different mechanisms for attacking diabetes may be more effective than one"). [Here,] Petitioner has not shown that it was well-known in the art that either [chemotherapy] or rituximab treat, i.e., attack [CLL in human patients.]

Pfizer, Inc. v. Biogen, Inc., No. IPR2017-01167, Paper No. 8, at 11-12 (P.T.A.B. Nov. 6, 2017).

Moreover, given that neither therapy was individually identified in the art cited in this ground as a potential treatment for CLL, in no way could the "combination of chemotherapy and rituximab [have been] one of a 'finite number of identified, predictable solutions' for treating CLL," Pet. 51, such that the combination would have been obvious to try. *See* § V.E.

VII. GROUND III: CLAIMS 46-57 WOULD NOT HAVE BEEN OBVIOUS OVER THE MALONEY REFERENCES, THE PRESS RELEASE, AND KIPPS

This ground fails for all the same reasons that Grounds I and II fail. *See* Sections V and VI. Moreover, as explained in further detail below, it would not have been obvious to administer to CLL patients rituximab in combination with any of the specifically enumerated chemotherapies of claims 46-57.

A. Ground III Fails For All The Same Reasons Grounds I And II Fail.

Petitioner states that claims 46-57 are obvious for the same reasons recited in Ground II, and that the Kipps textbook renders obvious the "specific chemotherapies" recited by each of these claims. Pet. 53. The art did not suggest administering rituximab to CLL patients, let alone administering rituximab-chemotherapy combination therapy in such patients, however, as discussed above in Sections V and VI. Accordingly, claims 46-57 would not have been obvious for all the same reasons Grounds I and II would not have

been obvious, including because Petitioner failed to establish that "the Genentech Press Release" is a prior art printed publication. *See* Sections V and VI. In addition, a POSA would not have been motivated to administer rituximab with any of the chemotherapeutic agents specifically recited by claims 46-57. *See* Sections V and VI.

B. The Art Did Not Suggest Combining Rituximab With The Chemotherapies Enumerated By These Claims To Treat CLL.

Petitioner never attempts to explain why a POSA supposedly would have chosen to combine rituximab with any of the specifically-claimed chemotherapies. Petitioner simply cites either (i) Kipps's extensive disclosure of chemotherapies that may be used in CLL patients, or (ii) the '612 patent specification's alleged disclosure of known chemotherapies, and asserts that it would have been obvious to combine any of those with rituximab in CLL patients. Pet. 54.

The law is clear that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co.*, 550 U.S. at 418. Petitioner failed to establish that a POSA would have selected any of the specific chemotherapies recited in claims 46-57 and combined them with rituximab to treat CLL patients with a reasonable expectation of success.

For example, Petitioner does not attempt to explain why a POSA would have chosen to combine rituximab with fludarabine (claim 53) or cyclophosphamide (claim 47). Instead, Petitioner refers (presumably) to the discussion of Maloney in Ground II as allegedly explaining why a POSA would have been motivated to combine rituximab and chemotherapy generally to treat CLL. Pet. 53. To the extent that Petitioner identified any motivation to use *any* chemotherapy in combination with rituximab for CLL (it did not, as explained in § VI.C.1), the motivation was that Maloney (via its interpretation of Demidem) suggested that rituximab *may* sensitize B-cell lymphoma cells from the DHL-4 cell line (not CLL cells). However, at most, a POSA interpreting Demiden's *in vitro* study in NHL cells would have been motivated to try using the chemotherapeutic agents that were actually tested in that study, which did not include either fludarabine or cyclophosphamide. *Id.*; *See also* Ex. 1032, 6-7.

Petitioner offers even less explanation as to why a POSA would have combined any of the claimed chemotherapies other than fludarabine or cyclophosphamide with rituximab to treat CLL. *See* Pet. 54. At most, Petitioner asserts that the claimed therapies were mentioned either in Kipps or in the '612 patent, and that Dr. Ozer testified that those compounds "were known to treat cancer." *Id*. (citing Ex. 1002, ¶ 107). Petitioner does not even allege that these compounds were known to treat CLL, nor does it offer any explanation as to

how and why a POSA would have combined them with rituximab to treat CLL as required by the claims. Accordingly, Petitioner fails to establish that any of the claimed combinations would have been obvious.

VIII. CONCLUSION

The Board should decline to institute *inter partes* review under any of Petitioner's proposed Grounds.

Dated: February 6, 2018

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

Pursuant to 37 C.F.R. § 42.24 (d), I certify that the present paper contains 13,662 words as counted by the word-processing program used to generate the brief. This total does not include the tables of contents and authorities, the caption page, table of exhibits, certificate of service, or this certificate of word count.

Dated: February 6, 2018

Respectfully submitted,

/s/ *Michael R. Fleming*
Michael R. Fleming

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. 42.6, the undersigned certifies that on February 6, 2018, a copy of the foregoing document and Patent Owners' Exhibits 2001-2010 were served by electronic mail upon the following:

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