UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Celltrion, Inc.
Petitioner,

v.

Biogen, Inc.
Genentech, Inc.
Patent Owners.

Case IPR2017-01230
U.S. Patent No. 7,682,612

PATENT OWNER PRELIMINARY RESPONSE

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I. INTRODUCTION

The claims of U.S. Patent No. 7,682,612 (the "'612 patent") describe effective methods of treating chronic lymphocytic leukemia ("CLL") through administration of an anti-CD20 antibody. Ex. 1001, 7:63-10:51. Petitioner challenges claims 1-13, 15-22, and 58-60 of the '612 patent on five different grounds. The Board should deny institution because Petitioner fails to establish that at least one document in each of the five grounds is a printed publication on which *inter partes* review may be based.

Grounds 1 and 2 are based on Ex. 1007, which Petitioner refers to as the "FDA Transcript" or the "Transcript." Petitioner offers no evidence—and does not attempt to argue—that Ex. 1007 was ever actually disseminated before the priority date. Rather, based on an unsworn letter from someone who does not even profess to have personal knowledge of Ex. 1007 before the priority date, Petitioner merely speculates that Ex. 1007 "would have" been received by a reading room before the priority date and the public could then have requested a copy. Moreover, Petitioner does not even assert, let alone offer evidence, that the "Transcript" also would have been catalogued or indexed such that a POSA exercising reasonable diligence could have located it in any such reading room. Accordingly, Petitioner never establishes that Ex. 1007 is a printed publication and Grounds 1 and 2 fail.

Grounds 3, 4, and 5 are based on Ex. 1061 and Ex. 1003, which Petitioner refers to as a print and online "MD Anderson Newsletter," respectively. Petitioner offers no firsthand testimony regarding the public accessibility of either document. If anything, the secondhand testimony offered by Petitioner shows that Ex. 1061 was ***never*** publicly accessible. As for Ex. 1003, Petitioner merely argues that it is prior art based on a date "last modified" appearing on it. Even assuming that the document was in fact "last modified" on that date, it would not follow that the document also was publicly accessible as of that date. Petitioner is therefore unable to establish that Ex. 1061 and Ex. 1003 are printed publications and Grounds 3, 4, and 5 fail too.

All five grounds would fail even if they were based on prior art printed publications. Grounds 1 and 2 would fail even if Ex. 1007 (the "Transcript") were a printed publication, for example, because Petitioner fails to show that the "Transcript," or any other document of the grounds, discloses or suggests administering to a patient with CLL any amount of anti-CD20 antibody, let alone an amount effective to treat the CLL, as claimed. Moreover, the one document of record that reported any results from actually administering rituximab to CLL patients before the priority date—Jensen (Ex. 1038)—would have discouraged a POSA from such administration, and would have foreclosed any reasonable

expectation of success, because it reported that administration of four weekly doses of 375 mg/m^2 rituximab resulted in a treatment failure accompanied by severe side effects and warned that even the 375 mg/m^2 dose "might be too high" for CLL patients. Ex. 1038, 004. A POSA would have been even more discouraged from practicing the methods of dependent claims 6 and 7, which require a dose even ***higher*** than that in Jensen: at least 500 mg/m^2. Petitioner fails to address Jensen.

Grounds 3, 4, and 5 would fail even if Ex. 1061 and Ex. 1003 (the "MD Anderson Newsletter[s]") were prior art printed publications because Petitioner is not able to show that all of the claim elements were found in those documents, or any of the other alleged prior art of the grounds. For example, Petitioner argues that a POSA would arrive at the biweekly and monthly dosing schedules of claims 19 and 20, respectively, based on routine optimization, but fails to make the required showing. Petitioner also fails to establish that a POSA would have had a reasonable expectation of success in arriving at the claimed inventions based on the "Newsletters"—especially in view of Jensen, which taught that rituximab was ineffective and even life threatening for CLL patients.

For these reasons, and as explained in detail below, the Board should deny institution on all grounds.

II. BACKGROUND

The ’612 patent issued from an application filed on November 9, 1999, and claims priority to U.S. Provisional Application No. 60/107,658 (the “’658 provisional application”), filed on November 9, 1998. Ex. 1001. The claims are directed to effective methods of treating chronic lymphocytic leukemia. *Id.*

A. Chronic Lymphocytic Leukemia

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. 2008, 001.

In CLL, the cancerous cell is a type of white blood cell known as a “B lymphocyte.” Ex. 2001, 003. These cancerous B lymphocytes proliferate and accumulate in the blood, leading to lymphocyte levels that are much higher than those found in healthy people. *Id.* A healthy person generally has no greater than 4,500 circulating lymphocytes per microliter of blood (“4,500 lymphocytes/µL”). *Id.* at 004. A CLL patient typically has a much greater number—and therefore is said to have “lymphocytosis.” *Id.* “[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"), at least 5,000 lymphocytes/μL is considered the ***minimum*** lymphocyte count for a CLL diagnosis. Ex. 1022, 003.

Although their acronyms may appear similar, CLL and SLL are distinct diseases. Unlike CLL, which is a leukemia, SLL, which stands for "Small Lymphocytic Lymphoma," belongs to a group of cancers called lymphomas. Specifically, it is one of the non-Hodgkin's lymphomas ("NHL"). Ex. 1018, 012.

A ***key*** differentiator between CLL and SLL is the level of circulating lymphocytes in afflicted patients, as reflected by lymphocyte count. Specifically, as set forth by the NCI Guidelines, "[t]he clinical diagnosis of CLL ***requires*** an absolute lymphocytosis [elevated lymphocyte count] with a lower threshold of greater than 5,000 mature-appearing lymphocytes/μL in the peripheral blood, in part to separate CLL from small lymphocytic non-Hodgkin's lymphoma." Ex. 1022, 003 (emphasis added); *see also* Ex. 1036, 006 (citing Ex. 1022, 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.

Petitioner cites to lymphoma classifications, namely the National Cancer Institute's Working Formulation ("IWF") and Revised European and American Lymphoma ("REAL") Classification, as allegedly equating CLL and SLL. Pet. 9. But IWF and REAL do not equate CLL and SLL. They simply describe SLL as "consistent with CLL," not identical to CLL, and describe SLL as ***lymphoma*** type "B-CLL/SLL." Ex. 1019, 006 (emphasis added); *see also id*. at 007; Ex. 1018, 012, 014. Further, unlike the NCI Guidelines for CLL, IWF and REAL lymphoma classifications merely address cellular morphology; they do not define what CLL is as a disease and how to differentiate it from other B cell diseases.[2]

[2] Petitioner repeatedly cites the Harris reference published in December 1999 (Ex. 1012) for the "conclusion" that "CLL and SLL are one disease at different stages, not two separate entities." Pet. 7. But that reference was published after the November 8, 1998 priority date of the '612 patent. Even if CLL and SLL were the same disease at different stages, it would not follow that treatment outcomes for one would be predictive of treatment outcomes for the other as explained in more detail below in SectionVI.A.2.b).

B. New Treatments For CLL

Although CLL is characterized by high circulating lymphocyte counts at the time of diagnosis, mere reduction in lymphocyte count is not sufficient to effectively treat CLL. Ex. 1022, 004. Instead, the goal of treating CLL is, and has been, to provide a positive clinical benefit to the patient, including 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). Ex. 1022, 004; *see also* Ex. 1055, 034.

While there were no proven cures for CLL in the 1990s, splenectomy, radiation therapy, marrow and blood stem transplantation, and various chemotherapies were used to treat CLL, but with limited success. Ex. 1055, 033-036.

The inventors of the '612 patent conceived of new treatments for CLL using anti-CD20 antibodies, including an antibody called "rituximab." Ex. 1001, 1:41-45. As set forth in the prosecution history, on August 15, 1995, '612 patent inventor Dr. Susan Desmond-Hellman emailed inventor Dr. Antonio Grillo-López regarding a "CLL study synopsis" that came out of a meeting held the same day. Ex. 1004, 735. The CLL study synopsis proposed treating CLL with rituximab

(also known as "C2B8") at dose levels of "150, 375, and 500" mg/m^2 and listed MD Anderson as a "Site[]" for conducting a study. *Id* at 735.[3]

A CLL study arising from this synopsis by these inventors was subsequently conducted by an external investigator, Dr. Susan O'Brien of the MD Anderson Cancer Center, under contract with Patent Owner.

III. THE '612 PATENT IS ENTITLED TO THE BENEFIT OF THE NOVEMBER 9, 1998 PRIORITY DATE

The '612 patent invokes priority to the '658 provisional application, which was filed on November 9, 1998. Petitioner does not dispute that claims 1, 5-7, 9, 11-13, 15-17, 21-22, and 59-60 of the '612 patent are entitled to the benefit of the November 9, 1998 filing date of the '658 provisional application. Pet. 19-22.

Petitioner argues that claims 2-4, 8, 10, 18-20, and 58 are not entitled to the November 9, 1998 filing date because these claims allegedly "lack written description or enablement support in the '658 provisional application." Pet. 20. Petitioner fails to carry its burden of proof on this issue.

[3] Petitioner acknowledges that this 1995 email suggested the use of 500 mg/m^2 of rituximab to treat CLL. Pet. 18-19.

A. Petitioner Bears The Burden Of Persuading The Board That Any Challenged Claims Are Not Entitled To The Benefit Of The November 9, 1998 Filing Date

Petitioner misstates the law when it asserts that "Patent Owners have the burden of demonstrating that 'a person of ordinary skill in the art would recognize that the applicant possessed what is claimed in the later filed application as of the filing date of the earlier filed application.'" Pet. 19 (quoting *Noelle v. Lederman*, 355 F.3d 1343, 1348 (Fed. Cir. 2004)).

A patent owner is not burdened with persuading the Board that a patent is entitled to priority. At most, a patent owner bears a burden of production on the issue of priority. *In re Magnum Oil Tools Int'l, Ltd.*, 829 F. 3d 1364, 1375-76 (Fed. Cir. 2016) (resolving "parties' arguments about the distinct burden of production"). If a Petitioner "has introduced sufficient evidence to put at issue whether there is prior art alleged to anticipate the claims being asserted," a patent owner bears the burden of "going forward with evidence either that the prior art does not actually anticipate" and/or "that it is not prior art because the asserted claim is entitled to the benefit of a filing date prior to the alleged prior art." *Technology Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327, 1329 (Fed. Cir. 2008).

It remains the petitioner's burden, however, to convince the Board that a patent owner "is ***not*** entitled to the benefit of the earlier filing date." *Id.* at 1328

(emphasis added); *HTC Corporation, et al. v. Advanced Audio Devices, LLC*, IPR2014-01158 (Paper 36) at 10 (Jan. 22, 2016) (emphasizing that "the ultimate burden of persuasion remains on the Petitioner," who must "convince the Board that the challenged claim is not entitled to the benefit of the earlier filing date").

B. The '658 Provisional Application Discloses That The Inventor Had Possession Of The Inventions Claimed

The '612 patent claims priority to the '658 provisional application, which was filed on November 9, 1998. Petitioner does not contest the chain of priority. Rather, as noted above, Petitioner argues that certain claims are not entitled to the benefit of the November 9, 1998 filing date of the '658 provisional application because these claims allegedly "lack written description or enablement" support in the '658 provisional application. Pet. 20.

As an initial matter, although Petitioner asserts that these claims "lack written description ***or*** enablement," *id.* (emphasis added), Petitioner does not offer evidence to support a conclusion that the claims are not enabled. Petitioner's expert does not even articulate the enablement standard, much less purport to apply it. Ex. 1005, ¶¶59-62. Furthermore, Petitioner's expert's assertions that "[a] POSA would not have understood the '658 provisional application to teach" "administration of an anti-CD20 antibody at a dose below 375 mg/m^2, . . . the administration of the anti-CD20 antibody weekly for any duration other than

4 weeks, or the administration of the anti-CD20 antibody on a bi-weekly or monthly schedule" are conclusory and misguided. *Id.*, ¶60. "[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); *Streck, Inc. v. Research & Diagnostic Sys.*, 665 F.3d 1269, 1288 (Fed. Cir. 2012) ("It is well established, however, that a specification need not disclose what is well-known in the art."). Neither Petitioner nor its expert identifies anything within the scope of the claims that a POSA allegedly would not have been able to practice based on the disclosure of the application and what was known in the art. Because Petitioner focuses on written-description arguments, so too does Patent Owner.

Under § 112, ¶1, "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." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). "[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id*. "The descriptive text needed [in the disclosure] to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic

knowledge already in existence." *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005).

"[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*, 598 F.3d at 1352; *Apple Inc. v. Papst Licensing GMBH & Co. KG*, IPR2016-01844 (Paper 10) at 16-17 (Mar. 10, 2017). "[T]he specification 'need not describe the claimed subject matter in exactly the same terms as used in the claims . . . .'" *All Dental Prodx v. Advantage Dental Prods.*, 309 F.3d 774, 779 (Fed. Cir. 2002) (quoting *Eiselstein v. Frank*, 52 F.3d 1035, 1038-39 (Fed. Cir. 1995)). "[Even] the failure of the specification to specifically mention a limitation that later appears in the claims is not a fatal one when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented." *Id.* at 779. The written description requirement is satisfied "when 'the essence of the original disclosure' conveys the necessary information—'regardless of *how* it' conveys such information." *Inphi Corp. v. Netlist, Inc.*, 805 F.3d 1350, 1354 (Fed. Cir. 2015) (emphasis in original).

With respect to claims 2-4 and 18-20, Petitioner argues that "the disclosures in the specification related to treating CLL only describe dosing rituximab at

375 mg/m^2 for four weekly infusions, and four weekly doses of rituximab at '375 mg/m$^{[2]}$' in week one followed by doses of '500-1500 mg/m$^{[2]}$,'" and "provides no other dosage regimens for treating CLL." Pet. 16-17 (internal citations omitted). The '658 provisional application proves otherwise. In fact, it discloses the limitations of claims 2-4 and 18-20 ***verbatim***.

Claims 2, 3, and 4 require that the anti-CD20 antibody is administered at a dosage of "about 0.001 to about 30 mg/kg," "about 0.01 to about 25 mg/kg," and "about 0.1 to about 20 mg/kg," respectively. The "Detailed Description Of The Invention" section states 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." Ex. 1002, 009. These ranges correspond expressly to the ranges found in claims 2, 3, and 4.

Claims 18, 19, and 20 require that the anti-CD20 antibody is administered "weekly for about 2 to 10 weeks," "biweekly," and "monthly," respectively. The application states that "[t]ypically, treatment will be effected weekly, for about 2 to 10 weeks," as expressly required by claim 18. Ex. 1002, 009; *see also id.* at 016 (original claim 6). Likewise, the requirements of biweekly and monthly administration in claims 19 and 20 appear expressly in the "Detailed Description

Of The Invention," which provides that administration of the anti-CD20 antibody "may be effected by various protocols, e.g., weekly, bi-weekly, or monthly, dependent on the dosage administered and patient response." *Id.* at 009.

Petitioner argues that there is "not a single example, reference study, or [any] demonstrated results" to support claims 2-4 and 18-20. Pet. 20-22. But no such subject matter is needed to satisfy the written description requirement. It is well established that "the written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement." *Ariad*, 598 F.3d at 1352; *see also Martek Biosciences Corp. v. Nutrinova, Inc*., 579 F.3d 1363, 1371 (Fed. Cir. 2009) ("[A] patent claim is not necessarily invalid for lack of written description just because it is broader than the specific examples disclosed."); *Tas v. Beachy*, 626 F. App'x 999 (Fed. Cir. 2015), *cert. denied*, 136 S. Ct. 1681 (2016) ("The PTAB correctly stated that the written description and enablement requirements do not demand as a matter of law actual examples or an actual reduction to practice.").

Petitioner further asserts with respect to claims 19 and 20, that the "[b]i-weekly and monthly dosing [limitations] are not discussed at all in the context of treating CLL." Pet. 22. But that, too, is incorrect, as shown above. The "Detailed

Description Of The Invention" section, in which biweekly and monthly dosing of the anti-CD20 antibody is disclosed, describes such dosing in the context of "administration of a therapeutic anti-CD20 antibody to treat . . . hematologic malignancies . . . characterized by high numbers of tumor cells in the blood." Ex. 1002, 005. The detailed description expressly states that "[t]hese malignancies include, in particular, CLL, B-PLL and transformed non-Hodgkin's lymphoma," *id.*, and that "[s]uch 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. Thus, bi-weekly and monthly dosing, as in claims 19 and 20, are clearly disclosed in the context of treating CLL.

IV. CLAIM CONSTRUCTION

A. "chronic lymphocytic leukemia" (CLL)

The term "chronic lymphocytic leukemia" in the claims of the '612 patent should be construed to mean "a B-cell cancer characterized in part by a threshold of greater than at least 5,000 lymphocytes/μL in the peripheral blood at diagnosis."

As discussed in Section II.A, the lower threshold for diagnosis of CLL as of the priority date was at least 5,000 lymphocytes/μL. Ex. 1022, 003 ("The clinical diagnosis of CLL ***requires*** an absolute lymphocytosis with a lower threshold of greater than 5,000 mature-appearing lymphocytes/μL in the peripheral blood, in

part to separate CLL from small lymphocytic non-Hodgkin's lymphoma.") (emphasis added).

Moreover, the threshold of at least 5,000 lymphocytes/μL is part of the intrinsic record. For example, during prosecution, Patent Owner's expert explained that "[t]he clinical diagnosis of CLL requires an absolute lymphocytosis with a lower threshold of >5 x 10^9 mature appearing lymphocytes per liter of peripheral blood [(5,000 lymphocytes/μL)]." Ex. 1036, 006 (citing Ex. 1022, 003). Patent Owner's expert also explained that "[t]his diagnostic criterion serves in part to distinguish CLL from small lymphocytic lymphoma (SLL)." *Id.*

The >5,000 lymphocytes/μL threshold also appears in the '612 patent's "References Cited," which constitute intrinsic evidence. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005) (en banc). For example, McLaughlin (Ex. 1016), which was cited during prosecution, Ex. 1001, 002, notes that "[p]atients with chronic lymphocytic leukemia," defined as patients with "lymphocytes >5 x 10^9/L" (>5,000 lymphocytes/μL), "were excluded" from the reported study. Ex. 1016, 004. The same threshold also was applied by inventors Drs. Grillo-López and White in a study reported in a 1997 paper by Maloney. Ex. 1015, 008 ("[P]atients with chronic lymphocytic leukemia (CLL) were

excluded from this trial (based on the presence of >5,000 lymphocytes/µL for this histologic subgroup).").

Petitioner's proposed construction reduces the minimum threshold from 5,000 ***lymphocytes***/µL to 4,000 ***white blood cells***/µL. Not only are these numerical differences significant, but the difference between "white blood cells" and lymphocytes is also significant. As Petitioner's expert explains, "[w]hite blood cells (also known as leukocytes) include" not only lymphocytes, but also "neutrophils, basophils, eosinophils, monocytes, and macrophages." Ex. 1005, 041 n.5. "Thus, [Petitioner's] threshold based on a white cell count of 4,000 cells/µL . . . corresponds to fewer than 4,000 lymphocytes/µL when based on lymphocyte count." *Id.* (emphasis omitted).

Petitioner tries to support its reduced threshold with reference to Example 3 of the '612 patent and the Batata and Kipps references. Pet. 23-24. But none of these materials supports Petitioner's positions:

Petitioner states that "[i]n Example 3 of the patent, CLL patients are identified as having '[m]edian white blood cell count [of] 40 x 10^9/L (range, 4-200).'" Pet. 24 (quoting Ex. 1001, 6:12-13). But that data is for previously diagnosed and treated CLL patients having lymphocyte counts subject to depletion by prior therapies. Ex. 1001, 012 ("Median numbers of prior therapies was 2.5

(range 1-9).”). Such data therefore does not set forth any threshold for diagnosing CLL in the first instance. Nowhere does Example 3 describe any of these CLL patients as newly-diagnosed based on any of the reported median white blood cell counts. The >5,000 lymphocytes/µL requirement is a threshold applied “at diagnosis,” as specified in Patent Owner’s construction, not a criterion applied dynamically to determine whether a previously-diagnosed CLL patient is somehow deemed to have CLL on any given day.

Contrary to Petitioner’s assertions, Batata and Kipps[4] do not offer “various thresholds” for diagnosing CLL and do not support a “>4,000 lymphocytes/µL” threshold either. Pet. 23-24. Even if they did support a 4,000 ***lymphocyte***/µL threshold, that is different from the 4,000 ***white blood cell***/µL threshold that Petitioner advances, as discussed above.

Batata describes a study in which “CLL was diagnosed according to the criteria established by the International Workshop on Chronic Lymphocytic Leukemia,” as set forth in two papers. Ex. 1008, 003 (citing Ex. 2002 and

[4] Notably, Batata and Kipps are extrinsic evidence. Even assuming they offered “various thresholds” for diagnosing CLL, this extrinsic evidence cannot negate the >5,000 lymphocytes/µL threshold set forth in the intrinsic record.

Ex. 2003). One of the papers states that "[d]efining criteria using the current staging systems for the disease suggest that a persistent lymphocytosis of >10 x 10^9/l [10,000/µL] is sufficient for a diagnosis of CLL," as is "lymphocytosis between 5 and 10 x 10^9/l [5,000-10,000/µL] [with supporting] cell marker studies." Ex. 2002, 005. The other paper states that "[l]ymphocyte counts in the blood are usually equal to or higher than 10 x 10^9/L [10,000/µL]" in CLL patients. Ex. 2003, 001. Thus, neither of these papers supports Petitioner's >4,000 white blood cells/µL construction.

Kipps states that "CLL invariably is associated with a blood ***lymphocytosis*** [>4,000 lymphocytes/µL (4 x 10^9 /liter)] whereas small lymphocytic lymphoma invariably is associated with lymph node involvement." Ex. 1055, 030 (brackets in original, emphasis added). This recitation of ">4000 lymphocytes/µL" is a definition of "lymphocytosis," not a definition of CLL. Elsewhere, Kipps describes >5,000/µL as the level of lymphocytosis that is required for a CLL diagnosis: "The diagnosis of CLL ***requires*** a sustained monoclonal lymphocytosis greater than 5,000/µL." Ex. 1055, 028 (emphasis added). In fact, Kipps adds, "[a]t diagnosis the absolute lymphocyte count generally exceeds 10,000/µL . . . and is sometimes greater than 100,000/µL." *Id.*

The Board should reject Petitioner's proposed construction and should construe "chronic lymphocytic leukemia" to mean "a B-cell cancer characterized in part by a threshold of greater than at least 5,000 lymphocytes/μL in the peripheral blood at diagnosis."

B. "effective to treat the chronic lymphocytic leukemia"

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

A United States District Court previously construed "effective to treat the chronic lymphocytic leukemia" this way in litigation involving the '612 patent. *Biogen Idec, Inc. v. Glaxosmithkline LLC*, No. 10-CV-00608-BEN (BGS), 2011 WL 4949042, at *2-3 (S.D. Cal. Oct. 18, 2011). In fact, the court addressed and resolved the exact issue facing the Board here, as explained in the opinion: "The parties agree that 'effective to treat [CLL]' includes the amount of [rituximab] that achieves a reduction in circulating tumor cells; the issue is whether a patient *must also* reach a positive clinical benefit in order for the treatment to be effective." *Id.* at *3 (emphasis in original).

Petitioner acknowledges the district court's construction, but argues that the Board should disregard it because the court was "[a]pplying a different claim

construction standard." Pet. 24 n.8. The court's construction was dictated by the prosecution history, however, and is accordingly the "broadest reasonable construction":

> The protocol of giving claims their broadest reasonable interpretation does not include giving claims a legally incorrect interpretation. Instead, claims should always be read in light of the specification and teachings in the underlying patent; the Board should also consult the patent's prosecution history in proceedings in which the patent has been brought back to the agency for a second review.

D'Agostino v. MasterCard Int'l Inc., 844 F.3d 945, 948 (Fed. Cir. 2016) (internal citations and quotation marks omitted).

1. The Prosecution History Mandates Patent Owner's Construction

The parties agree that the construction of "effective to treat [CLL]" should be based on the prosecution history. The parties disagree as to which construction the prosecution history mandates.

As explained below, the term "effective to treat the chronic lymphocytic leukemia" was added to the claims during prosecution to replace the phrase "effective to achieve a reduction in circulating tumor cells."

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. 2004, 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. 2005, 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.

"Claims are interpreted by reference to those that have been cancelled or rejected." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., LTD.*, 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." *Id.* Thus, "effective to

treat the [CLL]" cannot 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 1004, 648 (emphasis added) (internal quotation marks omitted). Along with this response, the applicants provided a declaration from Dr. 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. 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.*

The applicants also distinguished the claimed "effective[ness]" from the ineffective treatment described by Jensen (Ex. 1038). Ex 1004, 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 patient resulted in "severe side

effects," which the authors attributed to "rapid tumor lysis." Ex. 1038, 003-004. Three subsequent, weekly infusions were administered "without clinical problems," but, despite the initial normalization of the circulating lymphocyte count, the patient had progressive disease requiring salvage chemotherapy. *Id.* at 004. Jensen warns that "physicians must be aware of this hitherto unreported phenomenon in patients with high CD20-positive blood counts." *Id.* at 003. Similarly disappointing results were reported for an additional six patients. *Id.* at 004. 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*. As the applicant 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 1004, 648 (internal quotation marks omitted).

2. Petitioner Misinterprets The Prosecution History

Petitioner argues that "effective to treat the CLL [chronic lymphocytic leukemia]" means "a therapeutic response such as a reduction in the number of the small lymphocytic tumor cells." Pet. 24 (citing Andreeff Decl., Ex. 1005, ¶55). Petitioner premises its construction on a single statement made during prosecution:

"One of skill in the art of clinical oncology would understand that effective treatments of CLL include, but are not necessarily limited to, those assessed with respect to a reduction in circulating tumor cells." Pet. 24 (quoting Ex. 1004, 256) (emphasis omitted). Petitioner ignores the context of this statement, which was made in the same amendment where the applicants explicitly told the PTO that the new claims were directed to a different goal than "achiev[ing] a reduction in circulating tumor cells." Ex. 2005, 015. As the court in the earlier litigation observed, "[t]his statement does not contradict Plaintiffs' construction." *Biogen*, 2011 WL 4949042, at *5, n.6.

The statement that Petitioner relies upon simply asserts that effective treatments ***include*** "those assessed with respect to a reduction in circulating tumor cells." Ex. 2005, 015. In other words, while reduction in circulating tumor cells can be ***included*** as part of the assessment of therapeutic effectiveness, this alone is insufficient to show that a treatment is effective to treat CLL. *Id*. This in no way defines an effective treatment as any treatment that reduces circulating tumor cells only.

3. Reduction In Lymphocyte Count Does Not Amount To Effective Treatment

As explained above, as of the priority date, a POSA would have known that the goal of treating CLL was to provide a positive clinical benefit to the patient,

including 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). Ex. 1022, 004.[5] The NCI Guidelines specifically warned against using the absolute lymphocyte count as the sole indicator for treatment: "Therefore, the absolute lymphocyte count should not be used as the sole indicator for treatment, but should be included as part of the total clinical picture, which includes the lymphocyte doubling time . . . ." Ex. 1022, 007.

V. ALLEGED PRIOR ART

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

[5] As discussed in Section IV.A, the NCI Guidelines are part of the intrinsic record.

persons interested and ordinarily skilled in the subject matter or art[,] exercising reasonable diligence, can locate it." *Id.*

Petitioner has not made these showings with respect to two references: (1) the "FDA Transcript" (Ex. 1007) of Grounds 1 and 2; and (2) the "MD Anderson Newsletters" (Exs. 1061 and 1003) of Grounds 3-5.

A. Petitioner Fails To Establish That Ex. 1007 ("FDA Transcript") Is A Printed Publication

Petitioner offers no evidence, and does not attempt to argue, that the "FDA Transcript" was ever actually disseminated before the priority date. Instead, Petitioner attempts to show that an interested POSA would have been able to locate it. But the sole alleged evidence of the "Transcript's" purported public accessibility is Ex. 1054, a non-public letter from Ms. Dynna Bigby (the "Bigby Letter") that fails to establish the "Transcript" as publicly accessible such "that persons interested and ordinarily skilled in the subject matter or art[,] exercising reasonable diligence, [could] locate it." *SRI Int'l*, 511 F.3d at 1194.

The Bigby Letter is an unsworn FOIA Response letter—apparently generated in 2016 for this proceeding—addressing a request for "documentation to show that an advisory committee transcript was made available to the public on a specific date." Ex. 1054, 001. But the Bigby Letter provides no evidence whatsoever that the "Transcript" was catalogued or indexed such that a POSA

exercising reasonable diligence could have located it. Without such evidence, the "Transcript" cannot be considered sufficiently available to the public to constitute a printed publication. *In re Cronyn*, 890 F.2d 1158, 1161 (Fed. Cir. 1989) (explaining that references are not printed publications where they have not been publicly disseminated and have "not been either cataloged or indexed in a meaningful way").

The unsworn Bigby Letter, which lacks foundation to establish that Bigby has any personal knowledge regarding the assertions therein, states only that as of July 2016, the FDA had a copy of the "Transcript," and "[a]ccording to the procedures in place in 1997, the Division of Dockets Management (DDM) ***would have*** received the transcript on that [1997] date." Ex. 1054, 001 (emphasis added).[6] The Bigby Letter states that "[f]ollowing August 8, 1997, any member of the public ***could have*** requested and received a copy of the transcript in question by filling out a reading room request form." *Id.* (emphasis added).

[6] Notably, the Bigby Letter provides no evidence that the identified procedures that supposedly "would have" been followed were in fact followed for this particular transcript.

The Bigby Letter is silent regarding how a POSA allegedly would have known that the "Transcript" was available in the DDM reading room in the first place—or even that it existed at all. Petitioner offers no evidence that the hearing allegedly transcribed was "advertised or otherwise announced to the public," much less identified as a hearing for which a transcript would be made. *Samsung Electronics Co. Ltd. v. Rembrandt Wireless Technology*, IPR2014-00514 (Paper 18) at 6-7 (Sept. 9, 2014). Nor does Petitioner offer evidence that the contents of the DDM reading room was in any way searchable by the public, or that a POSA would have been aware of the DDM request process and how to follow it.

Even if it could be assumed that there was some search capability in the DDM reading room, that would not be enough to establish discoverability without details of such capability. In *In re Lister*, the Federal Circuit held that an article in a Copyright Office database that was searchable only by the author's last name and first word of the article's title was not sufficiently publicly accessible to be a printed publication. 583 F.3d at 1315. Here, the "Transcript" is titled only "Biological Response Modifiers Advisory Committee Nineteenth Meeting." Ex. 1007, 001. Even if the transcript had been indexed by title (the Bigby letter does not contend that it was), the title would have failed to inform a POSA because

it "bears no relationship to the subject" matter discussed therein. *In re Cronyn*, 890 F.2d at 1161.

Thus, the Bigby Letter provides no evidence that interested persons would have been able to locate the "Transcript," even with diligent effort. *Blue Calypso, LLC*, 815 F.3d at 1350; *see also*, *Groupon, Inc. v. Blue Calypso LLC*, CBM2013-00044, 2014 WL 7273564 at *11 (P.T.A.B. Dec. 17, 2014) (finding that a paper was not a printed publication where it "was only available for 'viewing and downloading' to members of the public who happened to know that the [] paper was there"). In effect, the "Transcript" is like a "poster[] at a vacant and unpublicized conference . . . available only to a person who may have [come across it] by happenstance or knew about [it] via unpublicized means." *SRI Int'l*, 511 F.3d at 1197.

Not only does the Bigby letter fail to establish that the "Transcript" was discoverable, it confirms that, if anything, the "Transcript" was not actually disseminated. It states that "[n]o requests were received for the transcript."

Ex. 1054, 001. Thus, Petitioner fails to carry its burden of establishing that the "Transcript" constitutes a printed publication.[7]

B. Petitioner Fails To Establish That Exhibit 1061 ("MD Anderson Print Newsletter") and Exhibit 1003 ("MD Anderson Online Newsletter") Are Printed Publications

1. Ex. 1061 ("MD Anderson Print Newsletter")

Relying ***only*** on the testimony of Dr. Andreeff,[8] Petitioner asserts that (i) "[i]n July 1998, MD Anderson published in print the Summer 1998 edition of its Leukemia Insights Newsletter ('MD Anderson Print Newsletter')" and (ii) "MD Anderson distributed printed copies of the MD Anderson Print Newsletter to several thousand Hematology-Oncology physicians in the U.S." Pet. 28 (citing Ex.

[7] Dr. Andreeff's testimony adds nothing. Citing only the Bigby letter, he simply states that "[t]he hearing was transcribed and, as confirmed by an official of the FDA, made available to the public on August 8, 1997." Ex. 1005, ¶63. Dr. Andreeff does not claim to have any knowledge, personal or otherwise, beyond that.

[8] Dr. Andreeff was employed by MD Anderson which, as noted above in Section II.B, conducted the CLL study described in the inventors' synopsis under contract with Patent Owner. Dr. Andreeff does not qualify as a "member of the public."

1005, ¶¶81, 83). But Dr. Andreeff does not purport to have any firsthand knowledge of this alleged publication or distribution.

Testimony regarding public availability of a document that is not based on firsthand knowledge does not establish dissemination sufficient to qualify a document as a printed publication. *See Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1330 (Fed. Cir. 2004) (finding "lack of substantial evidence of actual availability" where "there was testimony that it was the general practice at IADR meetings for presenters to hand out abstracts to interested attendees," but the witness "could not recall whether copies of the Abstract [in question] were actually available to hand out"); *Boehringer Ingelheim International GMBH, et al., v. Biogen Inc.* (Ex. 2010), IPR2015-00418 (Paper 14) at 11 (July 13, 2015) (finding Petitioner's contention regarding the public accessibility of a document was unpersuasive because it was based on an expert's testimony that did not assert any "firsthand knowledge of how, specifically, the [documents at issue] were distributed").

Dr. Andreeff concedes that his information is secondhand, stating only that he "understand[s] from Ms. Pierce" that a newsletter was mailed out to referring

physicians. Ex. 1005, ¶81.[9] Dr. Andreeff does not assert that he was involved in this alleged publication or distribution. He does not even assert that the "Newsletter" was "published in print" in July 1998 or that he received a copy of it in July 1998. Instead, Dr. Andreeff asserts that "[i]n 1998, doctors with patients seeking treatment for CLL routinely turned to MD Anderson to inquire about ongoing clinical trials" and speculates that as part of the clinical trial process "the Newsletter was disseminated to referring physicians, and they were free to share the information with their prospective patients." *Id.*, ¶83. These statements are merely hypothetical. Dr. Andreeff does not state that he disseminated the "Newsletter" to any referring physicians; nor does he identify a single example of another physician disseminating the "Newsletter." Even assuming Dr. Andreeff was motivated to "spread the word about the Newsletters," it does not follow that Dr. Andreeff actually disseminated the "Newsletter" as a matter of fact. *Id.*, ¶84.[10]

[9] Dr. Andreeff does not even state that Ms. Pierce claims to have mailed a copy of the "Newsletter."

[10] Of course, distribution of ***information*** contained in the "Newsletter" would not establish that the "Newsletter" itself was disseminated.

Further, there is no competent evidence that the "Newsletter" was mailed to anyone, let alone several thousand physicians in the Summer of 1998. For example, Petitioner does not provide a mailing list or even a mailed copy of the "Newsletter." There is in fact no evidence that more than a single copy of the "Newsletter" exists.

If anything, Dr. Andreeff's testimony makes clear that Ex. 1061 was ***not*** distributed to several thousand physicians and is ***not*** even an accurate copy of the newsletter that allegedly was distributed by MD Anderson. Dr. Andreeff states that he "obtained [Exhibit 1061] from Ms. Pierce" who allegedly "retrieved [Ex. 1061] from her files as [Dr. Andreeff] stood beside her." *Id*. Dr. Andreeff does not contend that Ms. Pierce obtained Ex. 1061 from someone outside of MD Anderson who received a copy in the mail. Rather, Ex. 1061 was allegedly always maintained in Ms. Pierce's files.

Further, Dr. Andreeff acknowledges that "the original printed date on [Exhibit 1061] appears to be 'Summer 1997'" but that date was changed to "'Summer 1998' by hand." Ex. 1005, ¶80. He reports that Ms. Pierce "explained that the originally printed date of '1997' was a mistake, and in the copy from her files, she had corrected the mistake by her own hand." *Id.* According to Dr. Andreeff, "Ms. Pierce did not catch that mistake in her review of the pre-print." *Id.*

"She only caught the mistake after the Newsletter had been mailed, and she changed the date on her copy for her MD Anderson files." *Id.* Thus, even assuming the "MD Anderson Newsletter" was mailed, Ex. 1061 is not an accurate copy of what was mailed.

2. Ex. 1003 ("MD Anderson Online Newsletter")

Petitioner offers no evidence, and does not attempt to argue, that the "MD Anderson Online Newsletter" was ever disseminated before the priority date. Instead, Petitioner attempts to show that an interested POSA would have been able to locate it because it allegedly was posted online before the priority date. But Petitioner has not established any such online posting or that the "Newsletter" was sufficiently publicly accessible such "that persons interested and ordinarily skilled in the subject matter or art[,] exercising reasonable diligence, [could] locate it." *See SRI Int'l*, 511 F.3d at 1194.

a) **Petitioner Fails To Establish That The "Online Newsletter" Was Posted To The Internet On Or Before July 2, 1998**

Petitioner alleges that Ex. 1003 is a copy of "[t]he Summer 1998 edition of the MD Anderson Online Newsletter" as it "appear[ed] in the Internet Archive Wayback Machine beginning February 8, 1999." Pet. 28. But February 8, 1999 was several months ***after*** the November 9, 1998 priority date.

Unable to produce any alleged archive data before the priority date, Petitioner points to the notation "Last modified on July 2, 1998" on the document allegedly from February 8, 1999, and to Dr. Andreeff's speculative testimony regarding the same. This is insufficient to establish that the "Newsletter" was publicly available on or before July 2, 1998.

According to Petitioner, "Dr. Andreeff explains that the content of the online newsletter would have been publicly available online as of the date of this 'last modified' date." Pet. 29. But Dr. Andreeff offers no such explanation. Instead, Dr. Andreeff merely states that the last modified date supposedly is "***consistent*** with [his] understanding that both the printed and online Newsletter were published around July 2, 1998." Ex. 1005, ¶82 (emphasis added). This is circular. Dr. Andreeff does not provide any basis for believing "that both the printed and online Newsletter were published around July 2, 1998" in the first place. Ex. 1005, ¶82. For example, Dr. Andreeff does not testify that he reviewed the "Newsletter" online in July 1998 or that he was involved in making the "Newsletter" available online at that time. Nor does Dr. Andreeff contend that the "Newsletter" actually ***was*** publicly available online as of this date.

Moreover, the "[l]ast modified" notation on the February 8, 1999 document is by no means determinative. Petitioner essentially argues that any webpage

bearing a "last modified" date should *per se* be deemed publicly accessible—and therefore a printed publication—as of that date. There is no such *per se* rule. *I-Blason LLC v. Aevoe Corp.*, IPR2016-00231 (Paper 9) at 5 (July 25, 2016) (finding that Petitioners failed to show that a document was a printed publication even though the relevant web page included the notation "last modified on February 2, 1999"). The cases cited by Petitioner do not suggest otherwise.

Petitioner cites *BLD Service, LLC v. LMK Technologies,* but the Board did not rely on a last modified date in that case. IPR2014-00770 (Paper 40) (Nov. 18, 2015). Rather, the Board found that sufficient evidence had been presented to establish that a reference, the De Neef Brochure, was publicly accessible where the petitioner submitted evidence "that [the] De Neef Brochure was made available as a PDF file on the internet by at least January 1, 2007" which was nearly nine months ***after*** the date last modified in the metadata of the PDF. *Id.* at 16 (indicating that the PDF "was last modified on '03/13/2006 6:57:02 PM'"). Moreover, the patent owner in that case did not contest that the brochure was published on the Internet by January 1, 2007. *Id*. If anything, therefore, *BLD Services* highlights that the last modified date should ***not*** be relied on to establish the date a webpage was posted online.

In *Stamps.com Inc. v. Endicia Inc.*, the last modified date was just one factor considered by the Federal Circuit. 437 F. App'x 897, 903 (Fed. Cir. 2011). "Other evidence confirmed the public availability of the article," including that "the article was catalogued by Carnegie Mellon University and listed as available on its indexed website in 1993 as 'CMU–CS–93–107.ps.Z.'" *Id.* "Significantly, [the last modified] date is several weeks ***after*** the date appearing in the article itself, suggesting that the website was not simply parroting the date appearing in the article." *Id.* (emphasis added). If anything, therefore, like *BLD Services*, *Stamps.com* highlights that the last modified date should not be relied on to establish a date posted.

b) **The Butler Affidavit Fails To Establish Even That The "Online Newsletter" Was Actually Available On The Internet On February 8, 1999**

Relying on the December 20, 2016 Affidavit of Christopher Butler (Ex. 1062) and its statements regarding how "[t]he Internet Archive assigns a URL on its site," Petitioner argues that Ex. 1003 was available online on February 8, 1999. Pet. 28 n.9. But the Butler declaration nowhere addresses Ex. 1003, and Petitioner offers no evidence that Ex. 1003 even came from the Internet Archive. Instead, Petitioner simply refers to "(Ex. 1003; accessed December 14, 2016)." Pet. 28. Notably, the URL appearing in the footer of Ex. 1003 differs from the URL of the

document attached as Exhibit A to the Butler Affidavit. *Compare* Ex. 1003, 001 *with* Ex. 1062, 004. Accordingly, Petitioner fails to establish that Ex. 1003 (or even Exhibit A to the Butler Affidavit) was posted to the Internet on or before February 2, 1999.

c) **Petitioner Has Not Established That The "Online Newsletter" Was Searchable Or Discoverable**

Even assuming the "Newsletter" was posted on a website as of July 2, 1998 or February 8, 1999, the Petitioner fails to present evidence demonstrating that a POSA or interested member of the public exercising reasonable diligence would have located it. For example, Petitioner offers no evidence regarding how any such website appeared on either date, or at any time before the priority date. Instead, Petitioner offers only what it contends is a single page from the website—in isolation. Ex. 1003.

Furthermore, Petitioner fails to offer evidence that any such website, any page on any such website, or any "Newsletter" posted to any such website, was indexed, catalogued, or searchable, let alone was a source that a POSA would seek out or search in the first place.[11]

[11] General statements about "turn[ing] to MD Anderson to inquire about [] on-going trials," even if true, do not establish that a POSA would have made such

Accordingly, Petitioner fails to establish that an interested researcher exercising reasonable diligence would have found any "Online Newsletter" before the priority date. This is fatal to Petitioner's argument that the "Online Newsletter" constitutes a printed publication. *See, e.g.*, *Blue Calypso, LLC*, 815 F.3d at 1349 (rejecting an argument that "an internet search engine would have been able to locate" a reference because 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 [reference] appearing in the search results"); *Microsoft Corp. v. Bradium Techs, LLC*, IPR2015-01435 (Paper 15) at 15-16 (Dec. 23, 2015) (rejecting a petitioner's argument that the Wayback Machine established a document as a printed publication and denying institution); *Cisco Sys. v. Constellation Techs.*, IPR2014-00871 (Paper 12) at 9 (Dec. 19, 2012) (finding an exhibit did not qualify as a printed publication even though it had been available on the Internet before the critical date because the petitioners did not present

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inquiry through a website, or by consulting any "Newsletter," much less that a POSA would have located any such website, or any "Newsletter" on such website, in the first place. *Cf.* Ex. 1005, ¶83.

evidence that "those interested in the art" would have known how to find the document).

VI. NO REASONABLE LIKELIHOOD THAT ANY CLAIMS OF THE '612 PATENT ARE UNPATENTABLE

A. Ground 1: Claims 1-13, 15-22, And 58-60 Are Not Obvious Over The "FDA Transcript," Batata, And Maloney

Petitioner argues that all challenged claims are obvious under §103 over the "FDA Transcript," Batata, and Maloney. The Board should reject this argument on multiple grounds.

1. Petitioner Fails To Establish That The "FDA Transcript" Was A Prior Art Printed Publication (All Challenged Claims)

Because Petitioner has not established that the "FDA Transcript" was a prior art printed publication, as explained in Section V.A, Ground 1 fails. *See Coalition for Affordable Drugs VIII, LLC v. Trustees of Univ. of Pennsylvania*, IPR2015-01835 (Paper 56) at 21-22 (Mar. 6, 2017) (finding that one reference in a proposed combination was not a printed publication, and as a result, concluding that Petitioner could not demonstrate that the proposed combination of references rendered the challenged claims obvious).

2. None Of "FDA Transcript," Batata, Or Maloney Discloses Effectively Treating CLL Patients By Administering An Anti-CD20 Antibody (All Challenged Claims)

Even assuming the "FDA Transcript" qualified as a prior art printed publication, Ground 1 would fail as to claims 1-13, 15-22, and 58-60 because it is premised on two fallacies: (1) that the "FDA Transcript" reported clinically meaningful results for administering rituximab to IWF Type A NHL patients; and (2) that those IWF Type A NHL patients were "SLL/CLL" patients. *See* Pet. 38.

As set forth in Section IV.B above, "effective to treat the chronic lymphocytic leukemia" requires that the treatment "provid[e] a positive clinical benefit to the chronic lymphocytic leukemia patient." The "FDA Transcript" does not show that rituximab tends to provide a positive clinical benefit even to SLL patients, let alone CLL patients.

a) **The "FDA Transcript" Did Not Report Clinically Meaningful Results For Administering Rituximab To IWF Type A NHL Patients**

Petitioner argues that rituximab had been shown to be effective in IWF Type A patients based on comments in the "FDA Transcript" about the results of a "pivotal study" in patients with low grade or follicular lymphoma (IWF Type A-D). Ex. 1007, 036; Pet. 33-35, 38. That study had particular "efficacy endpoints" agreed to in advance with the FDA. Ex. 1007, 037. The "primary efficacy endpoint[]" was the "overall response rate[,] with a goal of 35 to 40 percent, and as

secondary efficacy endpoints, time to progression in responders with a target of equal to or greater than 8 months, and duration of response with a target of equal to or greater than 6 months." *Id.* "As [Patent Owner] discussed with CBER [FDA's Center for Biological Evaluation and Research], a clinically meaningful result meant that you had to have an overall response rate of greater than or equal to 35 to 40 percent, a complete response rate of greater than or equal to 15 percent, and response duration of greater than or equal to 6 months." *Id.* at 083.

The "Transcript" reports that in the pivotal study the "overall response rate [was] 97 of 203 patients, that is, 48 percent," *id.* at 040, with "IWF Types B, C, and D patients [showing] a higher overall response rate of 58 percent." *Id.* at 043.

"[T]he study was not designed to show what the response rate was in the [IWF] Class A patients," *id.* at 068, which Petitioner equates to "SLL/CLL" patients, but the "Transcript" reported that those IWF Type A patients had a much "lower overall response rate at 11 percent." *Id.* at 044. Only "4 out of 37" IWF Type A patients responded. *Id.* at 117. The IWF Type A patients, as a group, therefore failed to meet (or even come close to meeting) the agreed-upon overall primary efficacy endpoint of 35 to 40 percent responders, and failed to achieve "a clinically meaningful result" under the definition articulated in the study itself. *Id.* at 037, 083.

Notwithstanding the failure of Type A patients to achieve the agreed upon primary efficacy endpoint, Petitioner argues that, according to Dr. Grillo-Lopez, "'these [Type A] patients, however, do have important clinical benefit,' including 'some tumor shrinkage' in 28 of the 37 Type A patients." Pet. 34 (quoting Ex. 1007, 044). But Dr. Grillo-Lopez makes clear in the "Transcript" that he was using the term "clinical benefit" broadly to encompass "some biological effect" on the patient. Ex. 1007, 071 (stating "so there is ***some clinical benefit***, there is ***some biological effect*** as manifested by the tumor reduction") (emphasis added). To be "effective" according to the claims of the '612 patent, however, a therapy must have more than just "some biological effect;" it must "provid[e] a positive clinical benefit," as discussed in Section IV.B above. As the '612 patent applicants explained during prosecution, "the claims do require a specific, positive therapeutic outcome, and not simply induction of any type of response in the patient." Ex. 1004, 613. Here, the "Transcript" fails to demonstrate any meaningful results for IWF Type A patients treated with rituximab.

Petitioner also argues that comments in the "Transcript" attributed to Dr. Ellin Berman allegedly evidence that rituximab was deemed effective to treat IWF Type A patients. Pet. 34. But, in fact, those comments were made precisely because no clinically meaningful results had been shown. Dr. Berman's comments

appear as part of a discussion of whether to ***carve out*** Type A patients from any FDA approval, given the paltry 11 percent (4 out of 37) overall response rate observed for such patients in the pivotal trial.

Three members of the Biological Response Modifiers Advisory Committee addressed this issue: Dr. Berman, Dr. Carole Miller, and Dr. Virginia Broudy. All three recommended no carve out. Dr. Berman opined that "11 percent is not to be disregarded" in the context of the discussion, "[s]o I would say that it does provide sufficient evidence of efficacy" to support not affirmatively carving off Type A patients notwithstanding the absence of clinically meaningful results. Ex. 1007, 117. According to the "Transcript," Dr. Miller stated that she "wouldn't break it down any further and say exclude[] this subgroup," but made clear that separate trials in the Type A patient population were needed. *Id.* ("I think whether or not what the long-term responses are going to be will be in other clinical practice trials that hopefully will be done in these patient populations."). Dr. Broudy warned: "I don't think we really have adequate data in this subgroup." *Id.* at 117-118. But she added: "I guess I would also not X these patients out, although I think it probably should say in the package insert that there was an 11 percent response rate in the initial trial with so many patients, and then the clinician can make his or her own judgment about whether to use this agent or not." *Id.*at 118.

Thus these individuals did not agree that rituximab had produced clinically meaningful results in IWF Type A patients. They merely agreed that IWF Type A should not affirmatively be excluded from a broader lymphoma indication to be approved.

b) **IWF Type A Patients Disclosed in the "FDA Transcript" Were Not CLL Patients**

Petitioner relies on the "FDA Transcript" as alleged evidence that rituximab was effective to treat CLL. Pet. 38. But none of the trials described in the "FDA Transcript" included CLL patients. In fact, those trials ***explicitly excluded*** CLL patients.

The "FDA Transcript" reports on results from the studies reported in Maloney (Sept. 1997) and McLaughlin. Pet. 33. Both studies expressly excluded CLL patients based on a ">5,000 lymphocyte/µL" threshold to define CLL—the same threshold found in Patent Owner's proposed construction for "chronic lymphocytic leukemia." Ex. 1015, 008. (reporting that "patients with chronic lymphocytic leukemia (CLL) were excluded from this trial (based on the presence of >5,000 lymphocytes/µl for this histologic subgroup)"); Ex. 1016, 004 ("Patients with chronic lymphocytic leukemia (lymphocytes >5 x 10^9/L) were excluded."); *see also* Ex. 1007, 081 ("No patients with CLL were included . . . .").

Petitioner tries to blur the line between CLL and SLL, seizing on the descriptions of patients as "IWF Type A patients" and stating that "IWF Type A patients were SLL/CLL." Pet. 38. But the "FDA Transcript" itself demonstrates that skilled artisans maintained the distinction between SLL and CLL, and recognized that the patients in the pivotal trial were SLL patients, not CLL patients. For example, Dr. Broudy refers in the "FDA Transcript" to "the lower response rate in ***the Working Formulation A, the small lymphocytic lymphoma patients***" in the pivotal trial. Ex. 1007, 068 (emphasis added).

Contrary to Petitioner's assertions, the "FDA Transcript" does not "explicitly contemplate[] the use of rituximab to treat patients diagnosed with CLL." Pet. 39. Petitioner bases its assertions on a statement by Dr. Grillo-Lopez and a statement by Dr. Berman, but neither statement supports Petitioner's position.

Dr. Grillo-López's statement about "also look[ing] at a small group of CLL patients" does not refer to study results from CLL patients who received rituximab, but rather to laboratory results characterizing CLL itself. Ex. 1007, 069. He made the statement in response to a question about whether the lower response rate in the "Working Formulation A, the small lymphocytic lymphoma patients [in the pivotal trial] . . . relates to the density of the CD20." *Id.* at 068. Dr. Grillo-Lopez answered

in the affirmative, reporting that "when we looked at our entire database of low-grade lymphoma patients and compared them to the Class A's, the Class A's tend to have a lower antigen density on the cell surface." *Id.* at 069. Dr. Grillo-Lopez then noted that "a lower and more heterogeneous CD20 expression" also was observed in "a small group of CLL patients, samples that we obtained courtesy of Dr. Susan O'Brien from MD Anderson Hospital." *Id.* That statement does not suggest that the studies reported in the "FDA Transcript" included CLL patients (they explicitly did not) or that further studies should.

Dr. Berman's statement that the pivotal trial "presumably" included "some [patients] with a lymphomatous phase of CLL," *id.* at 117, is a reference to patients with SLL, not CLL. "Lymphomatous" means "[p]ert[aining] to a lymphoma." Ex. 2009, 004. As Petitioner's own expert explains, patients with SLL have ***lymphoma***; patients with CLL have ***leukemia***. Ex. 1005, ¶28.

The "FDA Transcript" simply does not disclose or suggest treating CLL patients with rituximab. And Petitioner nowhere even contends, let alone demonstrates, that Batata or Maloney does either.

3. Petitioner Fails To Establish A Motivation To Combine The "FDA Transcript," Batata, And Maloney

Petitioner also fails to show "that a skilled artisan would have had reason to combine the teachings of the prior art references to achieve the claimed invention."

In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1068-69 (Fed. Cir. 2012).

a) **No Motivation To Treat CLL (All Challenged Claims)**

Petitioner argues that "[b]ecause it was known in the art that SLL and CLL are different tissue expressions of the same disease process, a POSA would have been motivated by the FDA Transcript's disclosure of the effective treatment of SLL/CLL to use rituximab to treat CLL patients specifically." Pet. 39. But CLL and SLL are ***not*** the same disease, *see* Section II.A, and the "FDA Transcript" does ***not*** even disclose that rituximab was deemed effective to treat SLL. *See* Section VII.A.2.a).

Moreover, contrary to Petitioner's assertions, a POSA would not have been motivated to use rituximab to treat CLL "based on the results of rituximab studies in NHL patients" generally. Pet. 40. Petitioner argues otherwise based on a "1995 Genentech press release" that states: "Genentech and IDEC are planning additional studies . . . in other B-cell mediated cancers such as intermediate grade NHL and chronic lymphocytic leukemia." Ex. 1034, 002. As an initial matter, Petitioner does nothing to establish that this "press release" (Ex. 1034) was "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence" could have located it,

SRI Int'l, 511 F.3d at 1194, and therefore fails to demonstrate that Ex. 1034 is a prior art printed publication. In any event, this is nothing more than a statement that further study is required and is insufficient to establish a motivation to combine. *Boehringer Ingelheim International GMBH, et al., v. Biogen Inc.* (Ex. 2010), IPR2015-00418 (Paper 14) at 18 (July 13, 2015) (holding disclosures that "at best, ***suggest potential rituximab treatments that require further study***" were insufficient to establish motivation to combine) (emphasis added) (internal citations omitted).

Moreover, by the November 1998 priority date, Jensen et al. had actually tried treating CLL with rituximab and the results were abysmal. As discussed in Section IV.B.1, Jensen is a "Rapid Communication" designed to warn POSAs that following administration of rituximab, a patient experienced severe side effects, including a reaction called "tumor lysis syndrome" (TLS), Ex. 1038, 003-004, which is potentially life-threatening. *See* Ex. 2006. Petitioner tries to downplay this warning by arguing that "[a] POSA would have anticipated the likelihood of TLS when attacking CLL and would have employed known techniques to minimize TLS." Pet. 40. That argument does not address Jensen's report that rituximab was also ***ineffective*** to treat CLL. Even after the administration of three further infusions of rituximab, the TLS patient had "progressive disease, requiring salvage

chemotherapy." Ex. 1038, 004 (reporting no effectiveness for any other patient either). A POSA would rate progressive disease as a "treatment failure." Ex. 1022, 008. This report would have discouraged a POSA from trying to use rituximab to treat CLL as of the priority date.

b) **No Motivation To Increase Dose (Claims 6-7)**

The trials described in the "FDA Transcript" administered rituximab at infusions of "375 mg/m^2." Ex. 1007, 036. Certain challenged claims of the '612 patent require administration of a high dose of an anti-CD20 antibody, such as rituximab, to CLL patients. For example, claim 7 requires that "the anti-CD20 antibody is administered to the patient at a dosage of about 500 mg/m^2."

Petitioner argues that "[a] POSA would have been motivated to dose rituximab at 500 mg/m^2" to treat CLL because "[i]n the FDA Transcript, Dr. Grillo-López states that IWF Type A patients 'may benefit from higher doses and/or more doses of the antibody [rituximab],'" and because "Maloney teaches that the 500 mg/m^2 is safe and may be effective." Pet. 41. But the IWF Type A patients disclosed in the "FDA Transcript" were SLL patients, not CLL patients, as discussed in Section VI.A.2.b) above. Indeed, CLL patients were excluded from the reported trials. *See id.* And Maloney did not administer 500 mg/m^2 doses of rituximab to any CLL patients—or SLL patients, for that matter. Ex. 1009, 005

(indicating the SLL patient was administered 50 mg/m^2 dose). Accordingly, a POSA would not have drawn from either the "Transcript" or from Maloney any motivation to administer rituximab to CLL patients at doses of 500 mg/m^2.

By the priority date in November 1998, the art taught away from—or at the very least provided no motivation to try—administering 375 mg/m^2 rituximab to CLL patients, let alone a higher dose. Jensen disclosed that even a 375 mg/m^2 dose was ineffective in CLL patients and caused dangerous side effects, as discussed in Section IV.B.1. In fact, Jensen expressly taught that such a "dose might be ***too high*** for the treatment of patients with substantial peripheral tumor load," such as CLL patients. Ex. 1038, 004 (emphasis added).

c) **No Motivation To Administer Biweekly Or Monthly (Claims 19-20)**

Petitioner fails to demonstrate that a POSA would have arrived at the biweekly or monthly schedules of claims 19-20 by combining the references of Ground 1. None of the references of Ground 1 describes dosing rituximab less frequently than weekly. Petitioner asserts that a POSA would have arrived at biweekly and monthly dosing schedules by routine optimization, but fails to make the required showing. There are at least five requirements that must be satisfied in order for "routine optimization" to apply to a variable, and Petitioner fails to establish that these requirements are satisfied.

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 either of the claimed biweekly or monthly administration schedules is in fact "an optimum," let alone that both are optimums, assuming that is even possible.

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 contend the administration schedule was considered "result effective," much less that a POSA knew how this variable allegedly affects results. *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 was also 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***.") (emphasis added). Petitioner fails to provide any evidence describing the experimentation process that allegedly would have been needed to arrive at the claimed dose schedule, much less evidence that such experimentation was known in the art.

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) (internal quotes omitted). Petitioner identifies no such suggestions in the art.

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 such experimentation would have been merely routine.

There is, therefore, no evidence that a POSA would have arrived at the claimed dose schedule through routine optimization and Petitioner's argument fails. Petitioner is actually relying on hindsight, not routine optimization. This is impermissible. *See, e.g., St. Jude Med., Inc. v. Access Closure, Inc.*, 729 F.3d 1369, 1381 (Fed. Cir. 2013) ("[W]e must guard against hindsight bias and *ex post* reasoning.") (internal quotes and cites omitted).

Petitioner points to Dr. Schenkein's statement, in a European Opposition proceeding, that "[s]uch less frequent schedules would have been readily adopted for the increased 500-1500 mg/m^2 dosages . . . particularly for combination therapy." Ex. 1049, 003. But Dr. Scheinkein was addressing whether biweekly or monthly dosages were "directly and unambiguously disclosed" by, and would have been readily adopted based on, a European counterpart to the '612 patent—not based on any prior art. *Id.* at 001. As explained by Dr. Schenkein, "the use of 'increased dosage' (500-1500 mg/m^2) rituximab for CLL was an important technical contribution of the patent in November of 1998." *Id.*

4. Petitioner Fails To Establish A Reasonable Expectation Of Success In Effectively Treating CLL (All Challenged Claims)

Petitioner devotes a total of only three sentences to addressing reasonable expectation of success in connection with Ground 1. And all three sentences are directed to the two independent claims. Petitioner does not even attempt to establish any expectation of success for dependent claims 2-5, 7-13, 15-22, and 59. Ground 1 therefore fails for at least the dependent claims.

With respect to the independent claims, Petitioner argues that "[a] POSA would have understood the FDA Transcript to demonstrate a detectable therapeutic response after four administrations of rituximab at 375 mg/m^2 in patients with SLL/CLL" and would have understood "Maloney to teach the safety and efficacy of administering rituximab at doses ranging from 50 mg/m^2 to 500 mg/m^2." Pet. 43. But neither the "FDA Transcript" nor Maloney discloses treating CLL patients, as discussed in Section VI.A.2.b). Further, the "FDA Transcript" does not demonstrate that rituximab is effective even to treat SLL, let alone CLL as

discussed in Section VI.A.2.a). And the only SLL patient in Maloney failed to achieve even a "Minor Response." Ex. 1009, 004.[12]

Only one study published before the priority date reported results from administering rituximab to CLL patients, and that was Jensen. Ex. 1038. As discussed in Section IV.B.1, Jensen reported that rituximab was ineffective and caused dangerous side effects. Petitioner fails to establish that a POSA would somehow have expected rituximab to successfully treat CLL notwithstanding the treatment failure reported by Jensen.

B. Ground 2: Claims 19-20 (biweekly and monthly dosing) Are Not Obvious Over The "FDA Transcript," Batata, Maloney, Byrd, And Kipps

As Ground 2, Petitioner argues that "[c]laims 19 and 20 are obvious over the FDA Transcript, Batata, Maloney, Byrd, and Kipps." Pet. 49. Ground 2 relies on all the references of Ground 1 plus two more: Byrd and Kipps. As explained in Section VI.A, Petitioner fails to demonstrate that the references of Ground 1 render

[12] Similar results were reported in subsequent trials involving SLL patients before the priority date. For example, Maloney (Sept. 1997) reported that one SLL patient dropped out of the trial due to adverse events. Ex. 1015, 006. Of the four remaining SLL patients, none had a clinical remission. *Id*. at 007.

obvious claims 19-20, or claims 1 or 6 from which both claims depend via claim 16. Petitioner does not even contend that Byrd and Kipps address the limitations of independent claims 1 or 6. Accordingly, Ground 2 fails for at least the same reasons that Ground 1 fails.

Ground 2 also fails because Petitioner falls far short of establishing that a POSA would have arrived at biweekly and monthly dosing. Petitioner argues, that "it would have been obvious to a POSA seeking to take advantage of rituximab's ability to chemosensitize chemotherapy-resistant NHL cell lines, as described by Byrd, to administer rituximab bi-weekly or monthly to align with [biweekly and monthly] chemotherapy administration." Pet. 50. This argument assumes that a POSA would be motivated to combine rituximab and chemotherapy in the first place. But, Jensen, which post-dates Byrd and Kipps, teaches against trying to treat CLL with rituximab at all, let alone in combination with chemotherapy.

Indeed, Jensen warned physicians that administering rituximab to CLL patients was ineffective; resulted in "severe side effects," including "rapid tumor lysis syndrome" (TLS); and still resulted in "progressive disease, requiring salvage therapy." Ex. 1038, 003-004. Like rituximab alone, chemotherapy alone has the potential to cause TLS or other infusion-related toxicities. *See, e.g.*, Ex. 2011, 001. A POSA would therefore have been concerned that combining rituximab together

with chemotherapy would exacerbate the potential for serious side effects even worse than those seen in Jensen where rituximab was administered alone. Because a POSA would not have been motivated to combine rituximab and chemotherapy to treat CLL, a POSA would have had no basis to modify the rituximab dosing schedule to "align with chemotherapy administration," let alone a reasonable expectation of success in doing so.

Petitioner also asserts that a POSA would have arrived at the biweekly or monthly administration by routine optimization, but fails to make the required showing, as discussed in Section VI.A.3.c) above. Instead, Petitioner points to Dr. Schenkein's statement. Pet. 52. Again, this statement relates to the teachings of a European counterpart to the '612 patent, not whether a POSA would have arrived at biweekly or monthly administration by routine optimization of any prior art, as discussed in Section Section VI.A.3.c) above.

C. Ground 3: Claims 1-7, 11-13, 15-18, 21-22, 59-60 Are Not Anticipated By The "MD Anderson Online Newsletter"

Petitioner argues that "[t]he method of treating CLL disclosed in the MD Anderson Online Newsletter meets all of the elements of claims 1-7, 11-13, 15-18, 21-22 and 59-60" and "because the MD Anderson Online Newsletter and the MD Anderson Print Newsletter have identical disclosures, these claims are equally anticipated by MD Anderson Print Newsletter." Pet. 56. But Petitioner fails to

carry its burden of proving that either Ex. 1061, the "MD Anderson Print Newsletter," or Ex. 1003, the "MD Anderson Online Newsletter," was a prior art printed publication. Section V.B. Thus, neither document can anticipate the claims of the '612 patent and Ground 3 fails.

Ground 3 would fail even if these documents were prior art printed publications because neither one discloses "providing a positive clinical benefit to [a] chronic lymphocytic leukemia patient" treated with rituximab, as required by the claims. Section IV.B. Indeed, both documents simply describe a study being initiated. Ex. 1061; Ex. 1003. No clinical responses are reported. Accordingly, Petitioner fails to establish that the "MD Anderson Print Newsletter" or the "MD Anderson Online Newsletter" discloses every limitation of claims 1-7, 11-13, 15-18, 21-22, and 59-60. "Anticipation requires that all of the claim elements and their limitations are shown in a single prior art reference." *In re Skvorecz*, 580 F.3d 1262, 1266 (Fed. Cir. 2009) (reversing finding of anticipation under broadest reasonable interpretation standard).

D. Ground 4: Claims 8-10, 19-20, And 58 Are Not Obvious Over The "MD Anderson Online Newsletter"

Petitioner argues that claims 8-10 and 58, which recite limitations related to the CLL patient's previous treatment, and claims 19 and 20, which include

limitations requiring biweekly and monthly administration, are obvious over the "MD Anderson Newsletter." Pet. 60-61.

1. Petitioner Fails to Establish That Any "MD Anderson Newsletter" Was A Prior Art Printed Publication (Claims 8-10, 19-20, And 58)

As with Ground 3, Petitioner fails to carry its burden of proving that either an online or print "MD Anderson Newsletter" was a prior art printed publication on which *inter partes* review may be based. Section V.B. Ground 4 therefore fails.

2. Petitioner Fails to Establish A Reasonable Expectation of Success In Effectively Treating CLL (Claims 8-10, 19-20, And 58)

Ground 4 fails even assuming that the "MD Anderson Newsletter" is a prior art printed publication. In connection with Ground 3, Petitioner argues that "[a] POSA would have had a reasonable expectation that the 500 mg/m^2 dose was 'an amount effective to treat CLL' in view of the MD Anderson ongoing trial." Pet. 55. To reach this conclusion, Petitioner relies on a statement from the MPEP that describes minimum thresholds for satisfying the ***utility*** requirement of 35 U.S.C. § 101. Specifically, the MPEP instructs the Examiner to presume that the utility requirement is satisfied if Applicant has initiated human clinical trials for a claimed therapeutic product or process. MPEP § 2107.03.IV. No such assumption applies to the requirement for a reasonable expectation of success.

The "MD Anderson Newsletter" reports that "a new monoclonal antibody approved for the treatment of lymphoma, is under investigation in patients with CLL." Ex. 1003, 004. This does not establish a reasonable expectation of success for such investigation. *See Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 619 F.3d 1329, 1338 (Fed. Cir. 2010) (explaining that a prior art reference disclosing a "bare proposal to use" the drug raloxifene in one clinical setting "is insufficient to require a finding that an ordinary skilled artisan would have expected that a compound with . . . known clinical failures—would successfully treat any human condition"). It is well known that clinical trials are, in fact, routinely unsuccessful. *See* Ex. 2007, 009 (showing that oncology trials are the least likely of all to be successful, as defined by advancement to the next phases of the approval process - 8.1% chance of advancing from Phase II to approval, 33% chance of advancing from Phase III to approval). Solely initiating or planning a trial would not have led a POSA to expect success.

Moreover, in NHL patients (including SLL patients), "[t]oxicity was mild" when a 375 mg/m^2 was administered. Ex. 1016, 003. By contrast, Jensen reported that this same 375 mg/m^2 dose was not well tolerated, but instead was toxic and ineffective, in CLL patients, as discussed above in Section IV.B.1. If anything, Jensen taught that 375 mg/m^2 was "too high." Ex. 1038, 004. In view of the

treatment failure reported in Jensen and Jensen's warning that a "dose [of 375 mg/m^2] might be ***too high***" for treatment of CLL patients, Ex. 1038, 004 (emphasis added), a POSA would not have reasonably expected that the 500 mg/m^2 dose proposed in the "Newsletters" was "an amount effective to treat CLL."

3. No Motivation To Administer Biweekly Or Monthly (Claims 19-20)

Petitioner also fails to demonstrate that a POSA would have arrived at a biweekly or monthly administration schedule. Again, Petitioner asserts that a POSA would have arrived at the dosing schedule by routine optimization, Pet. 61, but fails to make the required showing. *See* Section VI.A.3.c).

The "MD Anderson Newsletter" proposes "4 weekly infusions" with no discussion whatsoever of a less frequent dosing schedule. Jensen later reported that this same "4 weekly" dosing schedule resulted in treatment failure. Ex. 1038, 003. In view of the treatment failure reported in Jensen, there was no incentive to try an alternative, less frequent dosing schedule (bi-weekly or monthly as set forth in claims 19 or 20, respectively). Nor would a POSA have had a reasonable expectation of success that such less frequent dosing schedule would effectively treat CLL. Claims 19 and 20 are not obvious over the "MD Anderson Newsletter.

E. Ground 5: Claims 19-20 Are Not Obvious Over The "MD Anderson Online Newsletter," Byrd, and Kipps

Ground 5 relies on the "MD Anderson Newsletters" of Ground 4 plus Byrd and Kipps. Again, Petitioner fails to establish that any "MD Anderson Newsletter" was a prior art printed publication, as discussed in Section V.B. Accordingly, Ground 5 fails.

Even if the "MD Anderson Newsletter" were prior art, Petitioner would fail to demonstrate that a POSA would have arrived at the inventions of claims 19-20 based on its disclosure, as discussed in Section VI.D.3. Petitioner fails to remedy this defect with the addition of Byrd and Kipps. Petitioner's arguments again rely on the assumption that a POSA would have been motivated to combine rituximab and chemotherapy in the first place. But, as discussed in Section VI.B, no such motivation existed. Because a POSA would not have been motivated to combine rituximab and chemotherapy to treat CLL, a POSA would have had no basis to modify the rituximab dosing schedule to "align with standard chemotherapy administration," let alone a reasonable expectation of success in doing so.

Further, as discussed in Section VI.D.3, the treatment failure reported in Jensen and the weekly dosing schedule proposed in the "MD Anderson Newsletter" would have left a POSA without any incentive to try an alternative,

less frequent dosing schedule; much less a reasonable expectation of success that such less frequent dosing schedule would effectively treat CLL.

VII. UNCONSTITUTIONALITY OF *INTER PARTES* REVIEW

In *Oil States Energy Services LLC v. Greene's Energy Group, LLC*, 639 F. App'x 639 (Fed. Cir. 2016), *cert. granted*, 2017 U.S. LEXIS 3727 (June 12, 2017), the Supreme Court will consider the constitutionality of *inter partes* review proceedings. Patent Owner preserves the position that this *inter partes* review proceeding and the challenge to Patent Owner's duly issued and existing '612 patent violates the Constitution by allowing for private property rights to be extinguished through an adversarial process in the Patent and Trademark Office, a non-Article III forum, without a jury. *See McCormick Harvesting Mach. Co. v. C. Aultman & Co.*, 169 U.S. 606, 609 (1898) (once a patent is granted, "[i]t has become the property of the patentee, and as such is entitled to the same legal protection as other property.").

VIII. CONCLUSION

The Board should not institute *inter partes* review under any of Petitioner's proposed Grounds.

Dated: July 18, 2017

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 13,876 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: July 18, 2017

Respectfully submitted,

/s/Susan Langworthy
Susan Langworthy

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, the undersigned certifies that on July 18, 2017 a copy of **BIOGEN INC. AND GENENTECH INC.'S PATENT OWNER PRELIMINARY RESPONSE** and **EXHIBITS 2001 – 2012** were served in their entireties via electronic mail upon the following:

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