UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.

Petitioner,

v.

BIOGEN, INC.

Patent Owner.

Case IPR2017-01094
U.S. Patent No. 8,557,244

PATENT OWNER'S PRELIMINARY RESPONSE

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I. INTRODUCTION

The Board should decline to institute IPR2017-01094 because Petitioner failed to establish a reasonable likelihood that it would carry its burden to show that any claim of U.S. Patent No. 8,557,244 (the "'244 patent") is not patentable.

The '244 patent discloses and claims new methods for treating a vulnerable population of elderly patients with diffuse large cell lymphoma ("DLCL")—a particular type of intermediate-grade ("IG") non-Hodgkin's lymphoma ("NHL")—and who further present with large, or "bulky," tumors. The claimed treatment methods involve combining Patent Owner's therapeutic antibody rituximab with the chemotherapy combination known in the art as "CHOP."[1]

Before the priority date, those skilled in the art were greatly concerned that CHOP chemotherapy alone was ***highly toxic*** in elderly patients. Moreover, while rituximab had been approved for the treatment of ***low-grade*** NHL ("LG-NHL"), its results in intermediate-grade NHL ("IG-NHL") were not promising.

[1] CHOP refers to the combination of **C**ylcophosphamide, **H**ydroxydaunorubicin (also known as doxorubicin), **O**ncovin (also known as vincristine), and **P**rednisone. The combination of rituximab and CHOP is sometimes called "R-CHOP" therapy.

This was particularly so for patients with bulky IG-NHL tumors, where studies had shown that rituximab was unsuccessful. Against this backdrop, it was surprising and remarkable that the inventors were able to combine a chemotherapy believed to be unduly toxic in the elderly with an antibody shown to be ineffective in IG-NHL to create a safe and effective treatment for elderly DLCL patients whose disease presents with bulky tumors.

Petitioner challenges claims 1-2 of the ’244 patent on four different obviousness grounds, based on documents that it contends are prior art under § 102(b). Three of the grounds are based upon at least one reference that Petitioner fails to establish as a prior art printed publication on which *inter partes* review may be based.

Even if all of the references were printed publications, none of the grounds would set forth a reasonable likelihood that at least one of the claims of the ’244 patent is invalid. All of Petitioner’s proposed combinations involve selecting individual claim elements from disparate references and assembling them using hindsight. Petitioner offers no cogent reason why a POSA, as of the priority date, would have thought to make such combinations, much less would have expected success in doing so. The Board should deny institution on all grounds.

Ground 1

Petitioner argues that the claims are rendered obvious by the combination of Link (Ex. 1005), McNeil (Ex. 1006), and a document that it refers to as "the FDA Transcript" or the "Transcript" (Ex. 1010). This ground fails for at least four reasons.

First, Petitioner fails to establish that the "Transcript," which is the only reference that Petitioner relies on as purportedly teaching the "bulky disease" limitation, is a printed publication. Thus, the "Transcript" cannot render obvious any claims of the '244 patent, either alone or in combination with other documents.

Second, even assuming that the "Transcript" were a printed publication, Petitioner fails to identify in it, or any of the other prior art, any disclosure of treating the claimed patient population. Indeed, Petitioner fails to identify (in this or any other ground) even ***a single patient*** in the prior art who is within the claimed population of elderly DLCL patients whose cancer presents with bulky disease. Petitioner is at best able only to speculate—based on probabilities—that the studies it relies on "likely" included patients within the claimed population. Because this Board and the Federal Circuit have routinely held that inherency cannot be established by probabilities, this ground must fail.

Third, Petitioner fails to identify a reason for a person of ordinary skill in the art ("POSA") to combine the references to arrive at the claimed

invention. Though it offers a hodge-podge of rationales and unsupported assertions in an effort to piece together references teaching discrete claim elements, Petitioner has provided nothing other than hindsight as a basis upon which a POSA as of the priority date allegedly would have combined those disparate teachings. In fact, the art recognized that the elderly patient population treated by the '244 patent's claims did not tolerate intensive therapy well. This would have led the POSA away from combining CHOP chemotherapy with rituximab.

Fourth, Petitioner fails to establish that a POSA would have had a reasonable expectation of success in arriving at the claimed invention. The art actually pointed away from any such expectation. Indeed, the art recognized that the claimed elderly patient population responded to therapy unpredictably, and researchers "d[id]n't really understand why"—the polar opposite of circumstances leading to any reasonable expectation of success.

Ground 2

For Ground 2, Petitioner reiterates the arguments it made in Ground 1, relying on the combination of Link, McNeil, and a document that it refers to as "the 1997 Rituxan Label" or the "Label" (Ex. 1008), which it proposes as a fallback in case the Board finds, as it should, that the "Transcript" is not a printed publication. But Petitioner fails to establish that the "Label" is a printed publication too, rendering Petitioner's backstopping efforts futile. Even

assuming that the "Label" is available in this proceeding, however, the ground fails substantively for all the same reasons as Ground 1.

Ground 3

Petitioner argues that the claims are rendered obvious by what it refers to as "the E4494 Patient Consent Form" or the "Consent Form" (Ex. 1007) and the "Transcript." As noted above, the "Transcript" is not available as prior art in this proceeding, so the ground fails for that reason alone. Moreover, Petitioner also fails to establish that the "Consent Form" is a printed publication. Thus, none of the references cited in this ground are available in this proceeding. Even so, the "Consent Form" at most stands in for the limited teachings of Link and McNeil, which are themselves inadequate, as discussed above. Accordingly, Ground 3 substantively fails to render the challenged claims obvious for the same reasons as Ground 1.

Ground 4

As Ground 4, Petitioner repackages Link as a secondary reference and attempts to combine it with Sonneveld (Ex. 1009). This combination fails too. As with Grounds 1-3, the references in Ground 4, alone or in combination, fail to teach the effective treatment of even a ***single*** patient in the claimed population. At most, the new reference, Sonneveld, discloses the administration of CHOP alone to a small number of bulky disease patients that, by the admission of Petitioner's own expert, is "too few from which to draw a

conclusion about efficacy." As in Grounds 1-3, Petitioner fails to articulate a reason, other than hindsight, to combine the cited references. And again it fails to show that a POSA would have had a reasonable expectation of success in combining the cited references to achieve the claimed invention, particularly in light of the art-recognized difficulties and unpredictability in treating the claimed patients.

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

II. BACKGROUND

A. The '244 Patent and Prosecution History

The '244 patent issued on October 15, 2013, naming Christine White and Antonio Grillo-Lopez as inventors. Ex. 1001. The '244 patent discloses, among other things, new treatments for DLCL, which is a particular disease within the broader class of cancers known as NHLs. The patent claims the treatment of a distinct, high-risk, population of elderly DLCL patients whose disease presents with bulky (>10 cm in diameter) tumors. Claim 1 provides that these patients are treated with combination therapy comprising CHOP chemotherapy and an anti-CD20 antibody. Dependent claim 2 specifically provides that the antibody is rituximab.

B. NHL and its Treatment

1. NHL is a diverse group of diseases which differ significantly in prognosis and in treatment.

(a) IG-NHL is an aggressive and rapidly progressing form of NHL.

NHL is not a single disease. Rather, it encompasses "a diverse group of diseases ranging from the very aggressive and rapidly fatal to the more indolent." Ex. 2001, 4. Before the advent of the claimed methods, patients diagnosed with IG-NHL, of which DLCL—the specific lymphoma treated by the claims—is a subtype, "ha[d] an average survival rate of 2-5 years." Ex. 1001, 1:20-32. By contrast, LG-NHL patients "may survive an average of 5-7 years" from diagnosis." *Id*.

Because the clinical presentation and behavior of LG-NHL differs significantly from that of IG-NHL, the two categories of disease require different approaches to treatment and management. "Low-grade lymphoma usually presents as a nodal disease, and is often indolent or slow-growing." Ex. 2008, 4:49-52. By contrast, IG-NHLs are not localized to the lymph nodes, are aggressive and fast growing, and can spread rapidly throughout the patient's body. Ex. 1001, 1:29-35. While some IG-NHL patients did respond to the therapies known before the priority date, "they usually relapse[d] within several months." *Id*. at 1:40-42. Given the fast progression and short projected survival time for IG-NHL patients, there thus remained an urgent need in the

art for effective therapies that "decrease[d] the frequency of relapse." *Id*. at 1:65-2:2.

(b) Treatment of LG-NHL did not predict treatment of DLCL.

"Unlike the related disorder Hodgkin's disease, non-Hodgkin's lymphoma has firmly established cellular origin with morphologic subtypes corresponding to various stages of lymphocyte differentiation." Ex. 1044, 002. Thus, physicians have developed a number of classification systems in order to aid their diagnosis and treatment of NHL patients. These include the "International Working Formulation" ("IWF"), which "groups together the different non-Hodgkin's lymphomas according to their natural histories and responsiveness to therapy." *Id*. The IWF classifies NHLs generally as LG-, IG-, and HG-, and then further subdivides the classification based on tumor histology. *See Id*. at Table 1. DLCL is IG-NHL with IWF "Group G" classification. *Id.*

NHL classifications serve two key purposes. First, classifications must define "a ***distinct lymphoma subgroup*** and thus establish a proper diagnosis." Ex. 2003, 2.[2] Second, those distinct lymphoma subgroups "must be clinically useful and enable clinicians to estimate the prognostic relevance of this diagnosis and to guide therapeutic decisions accordingly." *Id*. Classifications

[2] Unless otherwise noted, emphasis added by Patent Owner.

like the IWF were "readily accepted by clinicians and . . . broadly applied." *Id.* at 3.

Treatment of NHL is tailored to the patient's particular type of NHL based on diagnoses informed by the histological classification of a patient's NHL. "[H]igh-grade lymphomas of all stages are generally treated with curative intention." Ex. 2002, 2. On the other hand, "final disease eradication cannot be achieved in low-grade lymphomas," with only a possible minor exception for some cases recognized early in their progression. *Id*.

Accordingly, a POSA would not have assumed that successful treatment of one grade of lymphoma would translate into successful treatment of a different grade. For example, shortly before the priority date it was reported that "[p]redictors of a favorable response to rituximab include indolent (IWF B, C, and D) histologies [and] nonbulky disease (largest lesion diameter <5 cm) . . . . ***The response data in intermediate and aggressive histologies to date have been less impressive***." Ex. 1028, 012. The Board previously recognized this principle in *Boehringer Ingelheim Int'l v. Biogen, Inc.*, No. IPR2015-00418, Paper No. 14 (the "Boehringer Decision"). In analyzing Patent Owner's '172 patent (Ex. 2008), the Board appreciated that those skilled in the art would not have applied disclosures regarding treatments for IG-NHLs to LG-NHLs, and vice versa. *See id.* at 18 ("Petitioner does not persuade us that it has explained adequately why an ordinary artisan would

have been encouraged to use rituximab maintenance therapy in a [LG-NHL] ***patient population distinct*** from [the IG-NHL patient population] described in McNeil."); *id.* at 21 (explaining "that a skilled artisan would [not] have understood that [approved LG-NHL] dosages were necessarily given in McNeil's study of ***intermediate grade NHL, a different patient population***.").

Fundamentally, NHL histology and morphology—the basis for classification—"are also the major determinants for treatment and prognosis." Ex. 2002, 2 ("histology [*i.e.*, grade] and stage still comprise the major determinants of therapy."). Indeed, the art of record further confirms that lymphomas of different classes respond to treatment very differently. For example, one clinical study of rituximab in LG-NHL patients showed a markedly different response pattern based on IWF classification, with significant differences in response for Grades B-D (Overall Response Rate ("ORR") 58%) as compared to Grade A (11%). Ex. 1014, 002. In other instances, clinical trials for patients with IG- and HG-NHL ruled LG-NHL patients ineligible for study and inclusion in the results, indicating that POSAs did not consider treatment of the different grades to be interchangeable. Ex. 1009, 004.

2. POSAs were concerned with CHOP's toxicity in elderly IG-NHL patients.

Before August 11, 1999, those skilled in the art expected poorer outcomes in elderly IG-NHL patients treated with CHOP owing to "more severe treatment related toxicity." Ex. 2009, 3. Such toxicity was attributed to an increased likelihood of concurrently present conditions, increased sensitivity to toxic drug effects, and altered chemotherapeutic drug pharmacokinetics. *Id*.; *see also* Ex. 2006, 10 (explaining that in elderly NHL patients, "toxicity may be enhanced, [and] many physicians believe that elderly patients are unable to withstand intensive chemotherapy."). Even CHOP chemotherapy ***alone*** was thought to be unduly toxic for certain elderly patients. Ex. 1006, 003 ("CHOP … is more toxic in this age group.").

3. Rituximab monotherapy was ineffective in treating IG-NHL, both with and without bulky disease.

Before the priority date, though rituximab monotherapy was found to be effective in a variety of LG-NHLs, it was not found to be effective in the more aggressive IG-NHLs. *See* Ex. 1028, 012 (reporting rituximab's success in treating LG-NHL but noting lack thereof in IG-NHL patients). In addition, at the time of the invention, while rituximab monotherapy was successful in treating bulky LG-NHL tumors, Ex. 1001, 7:30-35, studies indicated a total lack of success in using rituximab to treat patients with bulky IG-NHL (tumors ≥10 cm). Ex. 1015, 005 (Table 3).

III. CLAIM CONSTRUCTION

Petitioner attempts to significantly broaden the claims by advancing claim construction positions for the terms "[a] method of treating a patient" and "diffuse large cell lymphoma" that are inconsistent with the language of the claims and the intrinsic record. While the claims are to be given their broadest reasonable interpretation, *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016), "[t]he protocol of giving claims their broadest reasonable interpretation . . . does not include giving claims a legally incorrect interpretation." *D'Agostino v. MasterCard Int'l Inc.*, 844 F.3d 945, 948 (Fed. Cir. 2016) (quotations and citations omitted). "Instead, claims should always be read in light of the specification and teachings in the underlying patent," and the Board "should also consult the patent's prosecution history" in these proceedings. *Id.* (quotations and citations omitted); *see also In re Nuvasive*, Inc., No. 2015-1841, 2017 WL 2365257 at *4 (Fed. Cir. May, 31, 2017) ("[T]he Board's construction cannot be divorced from the specification and the record evidence . . . ."). The Board should reject Petitioner's unreasonably broad claim construction positions because they contradict the claim language as well as the understanding reached by Applicant and the Patent Office during prosecution.

Additionally, although Petitioner does not offer a claim construction for the term "bulky disease," the arguments in the Petition suggest that Petitioner

has applied an interpretation of the term that is inconsistent with its broadest reasonable interpretation. As such, Patent Owner addresses how this term would have been understood by a POSA.

A. The claims require effective treatment.

The claims recite "[a] method of ***treating a patient***." This language in the claims and specification describes a method that actually ***treats*** the patient's disease. It is not satisfied merely by ***administering*** rituximab and chemotherapy, contrary to Petitioner's suggestion. To construe the claim otherwise would contradict the teachings of the specification. *See* Ex. 1001, 2:9-14 ("[T]he present inventors have surprisingly found that rituximab, . . . already approved for the treatment of low-grade follicular non-Hodgkin's lymphoma, may be effective ***to treat*** more aggressive lymphomas as well."); 7:27-45 (evaluating treatment success based on patients' response rates to therapy).

The prosecution history confirms this understanding. For example, immediately preceding allowance, Applicant argued that Coiffier did not render the pending claims to "[a] method of treating a patient" obvious because it did not create a "reasonable expectation that a combination treatment with an anti-CD20 antibody, such as rituximab, and CHOP ***would be effective in treating patients*** with diffuse large cell lymphoma [and bulky disease]." Ex.

1002, 366. In the next Office Action, the Examiner allowed those claims in view of Applicant's arguments, stating that "Coiffier teaches that none of the patients with tumor lesions over 10 cm in size ***responded to treatment*** with rituximab." Ex. 1002, 372. Accordingly, both Applicant and the Examiner relied on the phrase "treating a patient" as requiring that the treatment be effective in the patient.

Petitioner gives excessive weight to the fact that claims presented earlier in prosecution also included a "therapeutically effective amount" limitation, which is not present in the issued claims. Pet. at 22. Petitioner acknowledges that during prosecution, Applicant explicitly argued that claims to "method[s] of treating a patient" using a "therapeutically effective amount" of rituximab required therapeutic effectiveness "in contrast to prior art allegedly describing an administration of antibody that lacked therapeutic effectiveness." Pet. at 22. But Petitioner ignores that Applicant continued to make (and the Examiner accepted) this same argument even after amending the claims to omit the redundant "therapeutically effective amount" limitation, because the effectiveness requirement was already expressed by the "method of treating" language. The broadest reasonable interpretation standard does not permit ignoring this prosecution history. *D'Agostino*, 844 F.3d at 949 (prosecution statements are "relevant as reinforcing the evident meaning of the claim

language at issue, whether or not [they] would meet standards for disclaimer or disavowal.").

B. Petitioner's proposed construction of "diffuse large cell lymphoma" contradicts the specification and prosecution history.

Petitioner proposes a construction for "diffuse large cell lymphoma" that contradicts the plain meaning of the claim, the specification, and the prosecution history. In particular, Petitioner proposes the construction: "diffuse large cell lymphoma, including diffuse large B-cell lymphoma under the REAL classification and diffuse large cell lymphomas previously defined as Grades F, G, and H under the IWF." Pet. at 23. Immediately following this proposal, Petitioner then notes that it anticipates that Patent Owner will argue that the term is limited to IWF Grade G NHL. While Petitioner's grounds of challenge fail under either construction, to the extent that the Board does construe "diffuse large cell lymphoma," it should reach the correct construction: "diffuse large cell lymphoma" means "diffuse large cell lymphoma" and does not also include "diffuse mixed cell lymphoma" (IWF Grade F) and "immunoblastic lymphoma" (IWF Grade H), which are different diseases.

A POSA reviewing the claims in light of the specification would understand that Applicant used the term "diffuse large cell lymphoma" according to its customary meaning, referring to a single, unique NHL subtype. *See* Ex. 1001, 2:41-48 (distinguishing "diffuse large cell lymphoma" from at

least 8 other NHL subtypes); 7:24-26 (distinguishing "diffuse large cell lymphoma" from "mantle-cell lymphoma); 8:13-15 (distinguishing "diffuse large cell" from "mixed" and "immunoblastic large cell histology NHL"). The specification explicitly states: "for the purposes of the methods described herein, intermediate- and high-grade lymphomas are defined as those designated in the 'Working Formulation' [i.e., the IWF classification] established in 1982." Ex. 1001, 2:38-42. As with the rest of the specification, the IWF classification distinguishes "diffuse large cell lymphoma"—a singular NHL subtype—from the other subtypes of NHL that Petitioner would like to sweep into the claims. *See id*., 2:38-48 (distinguishing numerous NHL subtypes). In short, both the text of the specification and the underlying classification system it references distinguish "diffuse large cell lymphoma" from other NHL subtypes.

Petitioner's construction also conflicts with clear statements in the prosecution history in which Applicant expressly and unambiguously limited the claim to "diffuse large cell lymphoma" and excluded diffuse mixed small and large cell lymphoma (DM) as well as immunoblastic large cell lymphoma (IBL). For example, in response to a rejection of then-pending claim 102, which issued as claim 1, Applicant argued that "[n]one of the patient group treated in the cited references is ***limited to patients with diffuse large cell lymphoma (grade 'G' lymphoma)***, ***as required by the language of [the]***

claim." Ex. 1002, 365. In light of this clear disavowal of NHLs other than DLCL, Petitioner's proposed construction, which includes Grades F and H (and perhaps more) cannot be correct. *See Purdue Pharma L.P. v. Endo Pharms., Inc.*, 438 F.3d 1123, 1136 (Fed. Cir. 2006) ("[P]atentee may limit the meaning of a claim term by making a clear and unmistakable disavowal of scope during prosecution.").

Finally, claims previously presented during prosecution further evidence Applicant's knowing exclusion of NHLs other than DLCL from the claims that issued. For example, originally presented claim 2 recited a method of treating various NHLs including "diffuse mixed small and large cell (DM) [Grade F], diffuse large cleaved cell (DL-C), diffuse noncleaved large cell (DL) [collectively, Grade G], [and] immunoblastic large cell (IBL) [Grade H]." *See* Ex. 1002, 21. When Applicant intended to include other grades of NHL in the claims, they were listed expressly. *See Clearstream Wastewater Sys., Inc. v. Hydro-Action, Inc.*, 206 F.3d 1440, 1446 (Fed. Cir. 2000) ("different words used in different claims result in a difference in meaning and scope for each of the claims").

C. The "bulky disease" recited in the claims is a characteristic of the patient's "diffuse large cell lymphoma."

The final limitation of claim 1 states: "wherein the patient . . . has bulky disease (tumor >10 cm in diameter)." Petitioner's grounds of challenge depend

on an erroneous implicit construction that assumes "bulky disease" is an add-on affliction or ailment, rather than a characteristic of how a particular person's DLCL presents.

In other words, bulky DLCL is not the same as bulky LG-NHL, because the underlying DLCL and LG-NHL are themselves clinically distinct. *See* Boehringer Decision at 18, 21. The "bulky disease" limitation does not refer to any type of tumor >10 cm. Rather, POSAs would understand from the language of the claim that the described patient presents with a >10 cm ***DLCL tumor***, and that the bulky disease referenced in the claim is a manifestation of the patient's DLCL. "Bulky disease" does not stand on its own apart from the type of cancer presenting in the patient. The specification confirms this understanding. *See* Ex. 1001 *at* 7:43-45 (describing use of rituximab to treat "intermediate- or high-grade NHLs ***accompanied by*** bulky disease.").

Petitioner's expert also confirms that bulky disease is a characteristic of a particular type of NHL presenting in the patient. For example, during prosecution, Applicant discussed the Vose study, which describes the treatment of patients with several NHL histologies, and reported results based on the size of the patient's largest tumor. Ex. 1024 at 006-007, Table 3. Dr. Lossos states that the cited portions of Vose were not informative as to whether there was

"therapeutic success in treating *DLCL patients with bulky disease*,"[3] because Vose "notes how many [of the various NHL] patients had bulky disease and provides response rates, ***but does not discuss whether these patients had DLCL.***" Ex. 1003, ¶117, n. 7. Accordingly, even Petitioner's expert understands that "bulky disease" is a characteristic of a particular NHL, and that the claims of the '244 patent require that the patient has bulky DLCL in particular.

IV. GROUNDS 1-3 EACH RELY ON AT LEAST ONE REFERENCE THAT PETITONER FAILS TO ESTABLISH AS A PRIOR ART PRINTED PUBLICATION

A patent claim can only be challenged in *inter partes* review "on the basis of prior art consisting of patents or printed publications." 35 U.S.C. § 311(b). "The determination of whether a document is a 'printed publication' . . . involves a case-by-case inquiry into the facts and circumstances surrounding its disclosure to members of the public." *Ford Motor Co. v. Versata Development Group, Inc.*, No. IPR2016-01019, 2016 WL 6678225 at *1 (P.T.A.B. Oct. 4, 2016) (citing *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004)).

Absent a showing of actual dissemination to those skilled in the art, the party seeking to establish a reference's "printed publication" status must prove that "a person of ordinary skill in the art interested in the subject matter of the

[3] Emphasis original.

patents in suit and exercising reasonable diligence would have been able to locate [it]." *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006).

Petitioner fails to make these showings with respect to at least three references: (i) the "Transcript" (Ex. 1010) utilized in Grounds 1 and 3, (ii) the "Label" (Ex. 1008) utilized in Ground 2, and (iii) the ECOG 4494 Patient Consent form (Ex. 1007) utilized in Ground 3.

A. Petitioner fails to establish that the "FDA Transcript" is a prior art 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, Ex. 1039 (the "Bigby Letter"), does not establish that the "Transcript" was publicly accessible such that an interested person exercising reasonable diligence could have located it. *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) ("public accessibility" is the touchstone in determining whether a reference constitutes a "printed publication."); *In re Lister*, 583 F.3d at 1311, 1313 (requiring that a reference must be "generally available" so as to "permit an interested researcher to locate and examine the reference").

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. 1039, 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 under Section 102. *In re Cronyn*, 890 F.2d 1158, 1161 (Fed. Cir. 1989) (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 in the letter, 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. 1039, 001.[4] The Bigby Letter states that "[f]ollowing August 8, 1997, any

[4] 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.

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.*

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." *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 were 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." 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 persons interested would have been able to locate the "Transcript," even with diligent effort. *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1350 (Fed. Cir. 2016). *See also, Groupon, Inc. v. Blue Calypso LLC*, No. 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 Intern., Inc.* 511 F.3d at 1197.[5]

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. 1039, 001.

[5] Petitioner's technical expert adds nothing. He simply characterizes the content of the insufficient Bigby Letter as his "understand[ing]," but claims no personal knowledge. Ex. 1003, ¶72.

B. Petitioner fails to establish that the "1997 Rituxan Label" is a prior art printed publication.

Petitioner also fails to establish that the "1997 Rituxan Label" was either disseminated before the priority date or was otherwise sufficiently accessible to the interested public. Petitioner asserts that "[t]he 1997 Rituxan Label was included in the packaging of Rituxan, which was approved by the FDA on November 26, 1997." Pet. 26. It cites two exhibits in support of this assertion: (1) Ex. 1008, which is what Petitioner refers to as the "1997 Rituxan Label" itself; and (2) Ex. 1029, which it characterizes as "a December 1997 10-K filing with the SEC." Pet. at 11.

Neither exhibit supports the first half of Petitioner's assertion—that "[t]he 1997 Rituxan Label was included in the packaging of Rituxan." Nowhere does Ex. 1008 itself claim to have been included in such packaging. And Ex. 1008 itself suggests that it is not a commercial package label because it contains what appears to be handwriting at the top of the document partially spelling "***Rit***uximab" in vertical orientation.

It is highly unlikely that a document with half the product name written in by hand was commercially distributed with Rituxan® vials.

As for Ex. 1029, nowhere does cited page 002—or any other page—even mention packaging, or the document of Exhibit 1008, or any package insert. Rather, it simply echoes only the second half of Petitioner's assertion—

that Rituxan® "was approved by the FDA on November 26, 1997." But that says nothing about the content of any accompanying package insert. There is simply no connection between Ex. 1029 and Ex. 1008.

The Board's decision in *Mylan Pharms. v. Boehringer Ingelheim Int'l GmbH*, No. IPR2016-01566, 2017 WL 506739 at *4 (P.T.A.B Feb. 3, 2017) is instructive. There, the "Petitioner contend[ed] that the Glucophage® Label qualifies as prior art under 35 U.S.C. §102(b) because it was approved and published by the FDA for treating type 2 diabetes in February 2001." *Id.* at *4. In its decision denying institution, the Board held that the purported label itself, without more, was insufficient to show it was a publicly accessible printed publication. *Id.* at 11. So too here. Ex. 1008 contains none of the hallmarks of a document published or disseminated before the priority date.

Moreover, even accepting as true Petitioner's statement that "[t]he 1997 Rituxan Label was included in the packaging of Rituxan," Petitioner offers no evidence as to ***when***, if ever, any package of Rituxan that allegedly included "[t]he 1997 Rituxan Label" was made publicly accessible. Petitioner states that the "Label is dated 'November 1997,'" Pet. 27, presumably referring to the copyright date at the bottom of page 002. But that is not evidence that it was publicly accessible as of that date. Indeed, the Federal Circuit has held that even an official certificate of registration from the Copyright Office does not

establish a document as a printed publication. *In re Lister*, 583 F.3d at 1312-13, 1317.

In sum, Petitioner's assertion that Ex. 1008 "qualifies as prior art under 35 U.S.C. § 102(b) because it was published and publicly available more than one year before August 11, 1999," Pet. 27, is a conclusion bereft of supporting evidence and fails to meet Petitioner's burden to establish that Ex. 1008 is a printed publication.

C. Petitioner fails to establish that the E4494 Consent Form is a prior art printed publication.

Petitioner argues that Ex. 1007 is a printed publication based on the Longo Declaration (Ex. 1004) but Dr. Longo's testimony does not establish that Ex. 1007 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] locate it." *SRI Int'l*, 511 F.3d at 1194.

Petitioner asserts that "Dr. Longo first received copies of the E4494 Protocol and Patient Consent Form from [his hospital's] data coordinators, who did not instruct him to keep any portion of the documents confidential." Pet. at 29. But Dr. Longo never states ***when*** he first received such copies, Ex. 1004, ¶32, nor does he contend that Ex. 1007 is one of those copies.

Petitioner next asserts that Dr. Longo "distributed the consent form to approximately ten prospective patients, every prospective patient who inquired

about the E4494 trial." Pet. 29. But again, neither Petitioner nor Dr. Longo state ***when*** such distribution allegedly occurred.

Citing Ex. 1051, Dr. Longo states that "[m]y ECOG-registered institution, the UWCCC, placed its first patient 'On Study' on September 14, 1998." Ex. 1004, ¶27. But conspicuously absent from Dr. Longo's declaration is any claim that he allegedly distributed a patient consent form to this "first patient." Dr. Longo presents no evidence that this particular patient (whom he does not claim was his patient) received the "Consent Form" before the '244 patent's priority date. Indeed, based on the document he relies on, Ex. 1051, that first patient was not even treated at Dr. Longo's "study site, UW Hospital and Clinics." *See* Ex. 1004 ¶33. Rather, the patient was treated at a site listed as, "Dean Health System, Hematology and Oncology Clinic." Ex. 1051, 002. No patient was on-study before the priority date at Dr. Longo's own study site; the first patient "on study" at UW Hospital and Clinics was in November 2000. *Id*. In short Dr. Longo offers no testimony from personal knowledge as to what documents were, or were not, provided any patient before the priority date.

In any event, Ex. 1051 at best establishes only that three patients may have received the "Consent Form" before the priority date. This is not sufficient to make Ex. 1007 a prior art printed publication even if it were assumed that the recipients were POSAs, not patients. *See Preemption Devices, Inc. v. Minnesota Mining & Mfg.*, 732 F.2d 903, 906 (Fed. Cir. 1984) (finding

that "dissemination of six copies" of a document to someone did not transform it into a printed publication where "[t]here is no evidence to show further dissemination by the [recipient] before the critical date").

Dr. Longo's passive assertion that "[i]t was expected that such patients would take the consent form home and discuss the pros and cons of the clinical trial with their own physicians, other oncologists who might provide second opinions, family members, friends, co-workers, and anyone else before deciding whether to enroll," Ex. 1004, ¶40, does not constitute evidence that such discussions ever occurred, much less that the "Patient Consent" form itself was "further disseminat[ed]." *See* Boehringer Decision at 8 (rejecting the argument that a letter mailed "to a single commercial entity" established that the letter "was publicly accessible so as to render it a printed publication under 35 U.S.C. §102(b)").

Nowhere does Dr. Longo state that he provided the patient consent form for E4494 to anyone other than prospective patients—and he does not say when he allegedly provided it to those patients. Nor does he assert that any of the prospective patients were "persons interested and ordinarily skilled in the subject matter or art." *SRI Int'l*, 511 F.3d at 1194. Thus, Dr. Longo's declaration fails to support his broad conclusion that "[t]he E4494 Patient Consent Form was distributed and discussed without any obligation or expectation of confidentiality starting by at least December 12, 1997, to any

physician, prospective patient, or any other person inquiring about the trial." Ex. 1004, ¶4.

V. Ground 1: Link in view of McNeil and the "FDA Transcript"

In this ground, Petitioner pieces together disparate teachings from three unrelated references to try to arrive at the claims of the '244 patent.

A. Because the "Transcript" is not available as prior art, the ground must fail.

The "Transcript" is the only reference that Petitioner relies on as purportedly teaching the treatment of patients with "bulky disease" of any kind.[6] Because Petitioner failed to establish that the "Transcript" is prior art, Ground 1 fails. *TRW Automotive U.S. LLC v. Magna Elecs. Inc.*, No. IPR2014-01348, Paper No. 25 at 12 (P.T.A.B. Jan. 15, 2016) ("Petitioner's ground of unpatentability ***necessarily fails***" when it relies on an unavailable reference); *Teva Pharms. Inc. v. Indivior UK Ltd.*, No. IPR2016-00280, Paper No. 23 at 8 (P.T.A.B. June 10, 2016) (a ground cannot be considered for institution if Petitioner fails to "provide[] a sufficient threshold showing that the [cited references] constitute prior art").

[6] Even so, Petitioner's argument relies on the inaccurate and unsupported conclusion, which even its own expert rejects, that a "bulky" indication is somehow interchangeable among clinically distinct diseases.

B. Link, McNeil, and the "FDA Transcript" do not teach the treatment of elderly DLCL patients with bulky disease.

1. Each reference individually fails to teach several claim elements.

(a) Link fails to teach the age and bulky disease limitations.

Link is a quarter-page abstract consisting of incomplete sentences that describe a pilot study of patients with IG- or HG-NHL treated with R-CHOP. Ex. 1005, 002. Of the 31 patients studied, 21 had Grade "G" NHL, as opposed to other histologically different subtypes. *Id*.; s*ee* §§ II.B.1, III.B.

Link provides minimal data on the ages of the patients studied, mentioning only a median patient age of 49 years old. Ex. 1005, 002. It is silent as to whether patients >60 may have been included, or if they were explicitly not studied via exclusion criteria. *See id.*

In any event, except for stating a median age of 49, Link does not say whether any patients over 60 were treated and thus does not satisfy the claims. Moreover even if Link's reported median age could be interpreted to mean that there was a "high" likelihood that at least some patients were over 60 (it cannot), inherency does not follow from any such likelihood. *In re Montgomery*, 677 F.3d. 1375, 1384 (Fed. Cir. 2012) ("[I]nherency does not follow even from a very high likelihood that a prior art method will result in the claimed invention."). A patient greater than 60 years old must necessarily

have been present in the study, as evidenced by the reference, in order to inherently satisfy the claim limitation; Petitioner fails to prove that one was.

Link is also completely silent as to the size of each patient's largest tumor (whether >10 cm or otherwise), and thus does not disclose that ***any*** of the patients treated in the study had bulky disease. Moreover, Link does not teach or suggest that any of the patients had DLCL (Grade G NHL) accompanied by bulky disease, regardless of age. Thus, Link is uninformative as to how patients with DLCL presenting with bulky disease would respond to its treatment regimen. Like the age limitation, the bulky disease limitation cannot be met inherently based on speculation. *See In re Jones*, 883 F.2d 1026, 1026 (Fed. Cir. 1989).

(b) McNeil fails to teach the bulky disease limitation and shows that the claims' success in elderly patients was unexpected.

McNeil is a short, high-level newsletter article in the Journal of the National Cancer Institute discussing difficulties in treating NHL in elderly patients. Like Link, McNeil contains no discussion of bulky disease, whether in DLCL patients, IG-NHL patients, or otherwise.

McNeil explained that "few clinical trials of any type have included older patients, a problem highlighted" by a contemporary editor's letter in the same publication. Ex. 1006, 003. This created a pressing medical need, as the incidence of NHL in elderly patients rose rapidly from 1973 to 1994, and it

was observed that "treatment for intermediate grade lymphoma—common among elderly NHL patients—is ***markedly less successful in older patients***." *Id*. Notably, McNeil states that CHOP is half as effective in elderly patients, and that being over age 60 is the most important factor independently associated with poor prognosis. *Id*.

McNeil goes on to describe a proposed study, which sought to compare CHOP vs. R-CHOP in IG- and HG-NHL patients over age 60 without identifying DLCL patients for treatment. *Id.* McNeil reports only that investigators had opened enrollment. *Id*. ("The new trial . . . ***will recruit*** 630 patients . . . ."). McNeil does not report that even a single patient had enrolled; it certainly does not report any data or results, let alone data or results suggesting successful treatment of a patient in the claimed population. And as discussed in further detail below in § V.D, the fact that the study was opening for enrollment does not speak to its results nor suggest to a POSA that it would be successful.

McNeil also describes ongoing studies seeking to find "other drug combinations that may be as effective but less toxic than CHOP" in elderly patients with aggressive NHLs. Ex. 1006, 004. Exemplary alternatives included the chemotherapies VMP, CTVP, and CIEP. *Id*. Accordingly, the inventors' choice to combine rituximab and CHOP in DLCL as claimed was not simply the selection of known approaches from a finite list of predictable solutions.

See Procter & Gamble Co. v. Teva Pharms. USA, Inc., 566 F.3d 989, 996–97 (Fed. Cir. 2009) (courts should not succumb to hindsight claims of obviousness where the only guidance in the art is at most an invitation to experiment). *See also* §§ V.C-V.D.

(c) The "FDA Transcript" teaches only the administration of rituximab monotherapy to LG-NHL Patients.

The final reference in Ground 1 is the "Transcript", which, for the reasons discussed in § IV.A, above, is not established as a printed publication. But even if it were, the "Transcript" describes a study in which all "patients were ***low-grade or follicular*** in histology [classes A-D]," and were treated with rituximab given "once weekly times 4 . . . over a 22-day period." Ex. 1010, 036. These LG-NHL patients are thus outside the scope of the claims even under Petitioner's overbroad construction of "diffuse large cell lymphoma."

Moreover, the results of the study show that even amongst patients with the same broadly classified type of NHL (*i.e.* low grade and follicular), histological type was one of three factors that had a statistically significant effect on ORR. In the study group, grade A patients had an 11% ORR, which was significantly lower than the 58% ORR for grades B-D patients. Ex. 1010, 044. Given this significant difference in response rate for NHL classes that were thought to at least be similar enough to be grouped together for study, the "Transcript" would have taught a POSA that one cannot simply extrapolate and

apply these results to predict what would happen if the protocol was applied to patients with IG- or HG-NHL. As was recognized in the art, NHL "is not a single disease," Ex. 2001, 4, and the response to treatment is very different across grades. *See* § II.B.1. Study results regarding the treatment of LG-NHL simply do not inform the POSA what will happen in treating IG-NHL, such as DLCL. *See* Boehringer Decision at 18, 21 (finding LG-NHL patient population distinct from IG-NHL patient population).

Petitioner relies on the "Transcript" primarily for its teachings regarding rituximab's potential effectiveness in treating bulky disease in LG-NHL patients. Pet. at 40-41. Just as the "Transcript" fails to provide any evidence of a correlation between treatment of LG-NHL and IG-NHL generally, it makes no suggestion that its findings with respect to rituximab's potential effectiveness in treating bulky ***LG-NHL*** would have informed a POSA's treatment of patients with bulky ***IG-NHL*** (including DLCL). Nor does Petitioner offer any evidence of such a suggestion. This is a fatal deficiency because the type of disease and the tumor size cannot be decoupled. § III.C.

Even if treatment of LG-NHL did inform POSAs how to treat DLCL (it does not), the cited portion of the "Transcript" does not even suggest that the rituximab treatment disclosed in the "Transcript" was effective for LG-NHL patients with bulky disease. The presenters did not report a statistically significant response in the group of LG-NHL patients with bulky disease; they

only provided anecdotal evidence that the results "approached significance." Ex. 1010, 045.

Furthermore, the data presented is not sufficiently disaggregated to allow appropriate analysis of bulky disease results. *See* Ex. 1003, ¶121. Indeed, Dr. Grillo-Lopez noted that the presenters had initial results from a study "***including*** patients with lesions greater than 10 cm, and that preliminary data . . . shows a 48 percent [10/21] response rate." Ex. 1010, 045-046. It is unclear if all 21 of those patients had lesions >10 cm, because the "Transcript" states only that such patients ***may*** have been included. Thus, the data cannot show how many of those patients (if any) were treated, and whether any of those patients responded to treatment.

2. The "FDA Transcript" fails to cure the deficiencies of Link and McNeil regarding the "bulky disease" limitation.

As explained in § III.C, the claims require treatment of a patient whose Grade G IG-NHL presents with bulky disease. But Petitioner relies exclusively on the "Transcript", which only discusses the treatment of LG-NHL, as allegedly disclosing this limitation.[7] Petitioner ignores the fact that "Transcript" teaches only the treatment of LG-NHL, and fails to discuss the

[7] As discussed below, Petitioner's appeals to legally improper inherency arguments do not cure this deficiency. *See* § V.B.2.

treatment of DLCL (much less bulky DLCL) in any fashion. Pet. at 40. This suggests that "bulky disease" is a standalone ailment (it is not) for which the "Transcript" proposes rituximab as a treatment (it does not). The claims specifically refer to "DLCL patients with bulky disease." Ex. 1003, ¶117; *see also* § III.C.

The "Transcript" at most teaches rituximab monotherapy as a treatment for LG-NHL presenting with bulky disease. This is wholly different from the patients required by the claim—namely patients with bulky DLCL, which is a form of IG-NHL. *See e.g.*, Boehringer Decision at 18, 21 (finding LG-NHL patient population distinct from IG-NHL patient population).

Petitioner's arguments for the inherent presence of bulky-disease DLCL patients in the cited art also fail. For example, Petitioner suggests that "Link and McNeil ***likely*** included patients with bulky disease," because reported data suggests that DLCL is characterized by bulky disease in 30% of patients. *See* Pet. at 40, 43. Petitioner cannot establish by probabilities that the presence of bulky disease in the particular patients studied is an inherent property of the population. *See PAR Pharms., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014) ("[T]o establish the existence of a claim limitation in the prior art in an obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art."); *Celltrion, Inc. v. Genentech, Inc.*, No. IPR2016-01667,

Paper 15 (P.T.A.B. Mar. 2, 2017) (finding with respect to a different patent that Celltrion's "inherency position is insufficient, as it is based upon probabilities.").

Since DLCL patients with bulky disease are never mentioned in the references, Petitioner's inherency argument is no better than a guess. *See In re Jones*, 883 F.2d at 1026. Determinations of obviousness must be based on what is known at the time of the invention, as evidenced by disclosure in the prior art. Petitioner has not established that elderly DLCL patients who presented with bulky disease were present in any of the studies discussed in Link, McNeil, or the "Transcript".

Accordingly, neither the "Transcript" nor Petitioner's inherency theory satisfy the bulky disease limitation. This is yet another independent reason why Ground 1 must fail.

C. Petitioner fails to articulate a reason to have combined Link, McNeil, and the "Transcript."

1. There is no basis for combining Link and McNeil to arrive at the combination of R-CHOP for elderly DLCL patients.

Petitioner argues that combining Link with McNeil is obvious simply because McNeil recognizes that the incidence if IG-NHL is high in elderly patients, and because Link recognized success with its method in younger patients. Pet. at 43-44. This ignores McNeil's teachings that part of the reason

for the lower efficacy of CHOP in elderly patients is that they do not tolerate it as well as younger patients, and that it "is more toxic in [the elderly] age group." Ex. 1006, 003; s*ee also* Ex. 2006, 10 (explaining that in elderly NHL patients, "toxicity may be enhanced, [and] many physicians believe that elderly patients are unable to withstand intensive chemotherapy.").

For example, McNeil further teaches that elderly patients cannot handle a full course of 6-8 CHOP cycles, which is a major factor in the population's worse prognoses. *Id*. In light of this express teaching that elderly patients cannot handle a full course of 6 doses of CHOP ***alone***, a POSA would not then apply the teachings of Link, which explicitly teaches that 6 doses of CHOP ***plus*** rituximab are needed. This certainly does not encourage the combination Petitioner suggests and in fact directs away from combining these two references. *See DePuy Spine, Inc. v. Medtronic Sofamor Danek. Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009) (a POSA would not "look past [McNeil's] warning regarding" elderly patients' inability to tolerate 6-8 doses of CHOP because McNeil "expresses concern for failure").

2. Petitioner fails to show that a POSA would have arrived at the claimed invention by "optimizing" the teachings of Link, McNeil, and the "Transcript".

The primary reason that Petitioner advances for combining the references is that a "POSA would have been motivated to combine the teachings of Link, McNeil, and the FDA Transcript to optimize therapy for

elderly patients with DLCL and bulky disease." Pet. at 42. Petitioner attempts to justify this rationale by citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007), arguing that the proposed combination "flows from the normal desire of scientists or artisans to improve upon what is already generally known."

In *Pfizer*, the issue was whether the besylate salt form of the drug amlodipine was obvious in light of prior art which taught to make salts of the drug, and the fact that "the genus of FDA-approved anions [the chemicals used to make drug salts] at the time was small." *Id.* at 1363. The Federal Circuit found an optimization rationale appropriate because "the only parameter to be varied [was] the anion with which to make the amlodipine acid addition salt." *Id*. at 1366. Further, *Pfizer*, unlike this case, was "not the case where the prior art teaches merely to pursue a general approach that seemed to be a promising field of experimentation or gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Id.* (quotations and citations omitted). Instead, in *Pfizer* the Federal Circuit observed that, "in selecting an acid addition salt formulation, one skilled in the art looked to pharmacopoeias and compendia to find a salt that was previously approved by the FDA and used successfully within the pharmaceutical industry." *Id*. In light of the finite group of acceptable candidates, which could be further narrowed, arrival at the claimed invention involved only "routine testing." *Id.* at 1367. Specifically,

"the prior art provided not only the means of creating acid addition salts but also predicted the results, which Pfizer merely had to verify through routine testing." *Id.* Petitioner is unable to show that the circumstances here are similar, particularly given that the art pointed away from using the therapies Petitioner alleges are obvious to combine, *see* §§ II.B.2-II.B.3, and given the recognized unpredictability in treating the claimed patients. *See* § B.1(b).

Petitioner's resort to "optimization" is driven by improper hindsight. Petitioner does not point to a single reference, or combination of references, that shows that the treatment of bulky disease in elderly DLCL patients was a problem that clinicians were trying to solve or "optimize" or "that [its] formulation of the problem was derived directly from the prior art, rather than from the challenged claims." *Purdue Pharma L.P. v. Depomed, Inc.*, 643 F. App'x 960, 966 (Fed. Cir. 2016). Nor does Petitioner point to anything in the prior art that "predicted the results" for DLCL patients. *Pfizer, Inc.*, 480 F.3d at 1367. Instead, it relies on disparate references teaching the individual elements of the claim, or at most that researchers were generally interested in treating elderly DLCL patients.

Additionally, selecting the claimed patient population, and then electing to treat them with rituximab and CHOP in combination, was not simply an optimization of a single parameter, like the type of salt used in *Pfizer*, or the identification of the optimum value of a particular parameter within a

numerical range. *See e.g.*, *In re Boesch* 617 F.2d 272, 276 (C.C.P.A. 1980) ("[D]iscovery of an ***optimum value*** of a result effective variable in a known process is ordinarily within the skill of the art.").[8] Here, at best "the prior art teaches merely to pursue a general approach that seemed to be a promising field of experimentation," a situation in which *Pfizer* instructs that an "optimization" rationale cannot suffice. 480 F.3d at 1366. In reality, the prior art did not teach a promising general approach for treating elderly DLCL patients with bulky disease at all: it taught uncertainty and unpredictability.

(a) POSAs would not arrive at the claimed population by "optimization."

Petitioner does not point to any reference that recognizes a problem with the treatment of bulky disease in the claimed population of DLCL patients. Indeed, Petitioner does not even cite evidence purporting to show the treatment of bulky disease in more aggressive lymphomas generally, let alone DLCL.

Petitioner must provide some reasoning or justification as to why a POSA supposedly would have looked to the treatment of disparate types of

[8] It does not appear that Petitioner is arguing that a POSA would arrive at the claimed methods by "routine optimization," though to the extent that it is, it has not come close to establishing the necessary factual predicates. Indeed, it has not even identified which of the many variables recited by the claimed method would be arrived at by an "optimization" process.

NHL to treat bulky disease such that there would have been a suggestion to POSAs to apply treatments used in LG-NHL to IG-NHL. It has not done so here. *See* §§ II.B.1, V.B.2; Boehringer Decision at 18, 21 (finding LG-NHL patient population distinct from IG-NHL patient population).

(b) It would take more than "optimization" to arrive at the claimed therapy.

Even assuming that Petitioner has established that CHOP was the standard therapy for elderly DLCL patients whose DLCL presented with bulky disease (it has not), Pet. at 44, and even assuming that a POSA would have sought to "optimize" the therapy of such patients, Petitioner fails to show that it would have taken nothing more than "routine optimization" to arrive at the claimed R-CHOP regimen. Most critically, "routine optimization" only applies where there is an art-recognized "result-effective" variable. *See e.g.*, *In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977). But Petitioner does not even identify the variable to be optimized, let alone how to modify it to arrive at "an optimum." In fact, there are a number of unidentified variables at issue here rendering an optimization rationale especially inapplicable.

A POSA might have questioned whether to modify how CHOP is administered (*e.g.* by changing dosage and frequency) or whether to combine it with additional therapies. Upon deciding to pursue a combination therapy, a POSA might have next asked which additional therapies to add. There were

many options available in the art, and the POSA would have had to decide amongst adding additional chemotherapeutic agents, radiotherapy, monoclonal antibodies, or other biologic therapies. *See* Ex. 1001, 1:44-2:44. Even assuming the POSA would have decided to use a monoclonal antibody, the POSA would have then had to choose the antibody. There were many to choose from in the art targeting NHL-afflicted B-cells in a variety of manners. *Id.*

Accordingly, Petitioner fails to provide any evidence describing the process that allegedly would have led to the claimed combination therapy for the claimed patient population, much less evidence that such experimentation was known in the art. To the contrary, the art of record suggests that any such experimentation process would be far from "routine" due to the recognized difficulties in studying elderly patients. *See Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989) (internal quotes omitted) (optimization requires the art to "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."); §§V.B.1(b).

Petitioner relies on hindsight, not so-called optimization. The Board should reject Ground 1.

D. Petitioner fails to establish that a POSA would have had a reasonable expectation of success in combining these references to treat elderly DLCL patients presenting with bulky disease.

Petitioner also fails to show, as it must, "that a skilled artisan would have had reason to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012). "The reasonable expectation of success requirement refers to the likelihood of success in combining references ***to meet the limitations of the claimed invention***." *Intelligent Bio-Systems v. Illumina Cambridge*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

Petitioner's failure to show a reasonable expectation of success is particularly apparent 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. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). Indeed, the cited art highlights the unpredictability of the claimed patients: "The elderly have a higher relapse rate . . . **and we don't really understand why**.'" Ex. 1006, 004. This is the antithesis of a reasonable expectation of success.

Petitioner attempts to bolster its expectation of success arguments by referring to the inventors' own appreciation and interpretation of prior studies—in which they were involved. Petitioner's reliance on the inventors themselves is misplaced; the law recognizes that inventors possess knowledge "which sets them apart from the workers of ordinary skill." *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985). There is no factual or legal basis, other than impermissible hindsight, for Petitioner's attempt to impute the inventors' unique perspective to POSAs. *See Life Techs. Inc. v. Clontech Labs, Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000) ("That the inventors were ultimately successful is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success."). Ultimately, Petitioner has pointed to no evidence showing that a POSA would have a reasonable expectation of successfully treating DLCL presenting with tumors >10 cm in an elderly patient by administering R-CHOP.

1. Petitioner has not established the successful treatment of the claimed patient population.

Petitioner has not identified a reference, or combination of references, that targets the claimed patient population, and thus provides no basis why a POSA would expect to successfully treat bulky DLCL in a patient older than 60.

Link fails to provide a reasonable expectation of success because it is silent as to whether one would expect that R-CHOP would be successful in the claimed population. As discussed in § V.B.1(a), the Link study focuses on a group of patients that appears to skew younger than the general population of DLCL patients and does not address whether elderly patients were included at all. Accordingly, POSA's would not reasonably have expected this data to be predictive of results in the elderly population, particularly in light of McNeil's statements that (i) elderly patients have not been studied; and (ii) elderly patients react more unpredictably (and unfavorably) to intensive treatment.

Dr. Lossos's testimony does not cure the factual deficiencies of the record. He is able only to reiterate Link's unsupported conclusion that "combination therapy 'may offer higher response'" rates. He provides no explanation of how POSA's would have applied this statement, if at all, to different patient populations (i.e. to the claimed patient population). Further Dr. Lossos does not explain why this conclusion should be treated as anything other than Link's self-interested call for additional research, for example, since the treatment ***may not*** offer higher response rates. Ex. 1003, ¶91.

2. The opening of enrollment for the E4494 study does not suggest a reasonable expectation of success.

Petitioner next argues that the opening of the E4494 study (as described by McNeil) for enrollment provides evidence that a POSA would have had a

reasonable expectation of success. But the E4494 study disclosed in McNeil fails to teach all limitations of the claim; it is totally silent as to the presence of patients with bulky disease (let alone the successful treatment of that population).

Further, McNeil reports on only the commencement of (or opening of enrollment for) a clinical trial. This does not establish a reasonable expectation of success. *See Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 619 F.3d 1329, 1338 (Fed. Cir. 2010) (a reference's "bare proposal to use" a drug does not establish a reasonable expectation of success). Similarly, McNeil's bare proposal to use R-CHOP in patients >60 years old, while at the same time recognizing the unpredictability and lack of success of various therapies in treating this population, shows that POSAs would have been pessimistic about successfully treating those patients.

A POSA would have understood that clinical trials are, in fact, routinely unsuccessful. *See* Ex. 2007, 9 (showing that oncology trials are the least likely of all to be successful, as defined by advancement to next phase of approval process). McNeil's report that the trial opened for enrollment would not lead a POSA to expect to success, since on the publication date, the study had not treated a patient and reported no results.

Petitioner also exaggerates the significance of McNeil's report when it argues that a "POSA would have presumed that the treatment method

investigated by the large ECOG clinical trial described in McNeil was reasonably likely to have therapeutic utility." Pet. at 45. To reach this conclusion, Petitioner erroneously relies on MPEP § 2107.03.IV, which describes minimum thresholds for satisfying the ***utility*** requirement of 35 U.S.C. § 101. But here—in the context of Section 103—the burden is on Petitioner to affirmatively show reasonable expectation of success. *See Institut Pasteur v. Focarino*, 738 F.3d 1337, 1344 (Fed. Cir. 2013) (Where one of ordinary skill in the art would not have "reasonably predicted the successful adaptation of" the prior art to yield the claimed invention, there is not a sufficient expectation of success to support a finding of obviousness.). That a study intended to proceed in spite of known difficulties in treating elderly patients does not indicate a reasonable expectation of success. *See In re Brimonidine Patent Litig.*, 643 F.3d 1366, 1376 (Fed. Cir. 2011) (where prior art recognizes significant "roadblocks" present on the route to the claimed invention, "one of ordinary skill would not have been expected to disregard [them]" to have an "anticipated success" that a proposed combination of references would work).

3. Evidence regarding treatment of bulky LG-NHL does not suggest that similar treatment would be successful in bulky DLCL.

Petitioner provides no evidence that the non-analogous "Transcript's" disclosures "regarding rituximab treatment of low-grade NHL accompanied by

bulky disease would have increased a POSA's expectation of success." Pet. at 46. Neither Petitioner nor Dr. Lossos explain why a POSA allegedly would have looked at treatments of what were known to be different diseases, *see* §§ II.B.1, V.B.2, to arrive at the claimed invention. Petitioner instead relies on hindsight. This reliance on hindsight is particularly evidenced by Petitioner's statement that "[a] POSA reviewing the data in the FDA Transcript would likewise have concluded that rituximab, particularly when combined with CHOP, would be useful for treating bulky tumors in patients with DLCL." Pet. at 46.

This is nothing but hand waving. The "Transcript" does not mention DLCL at all, and discusses single agent studies—not combination therapy. Petitioner articulates no reason, based on information that would have been known before the priority date, to combine all of these disparate elements to arrive at the claims. *See Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1066 (Fed. Cir. 2016) ("the Board must still be careful not to allow hindsight reconstruction of references . . . without any explanation as to *how* or *why* the references would be combined to produce the claimed invention.") (citations and quotations omitted).

The evidence of record further shows that skilled artisans recognized that different grades of NHL responded to treatment differently and that one could not assume that a treatment necessarily would work in one NHL class

solely because it was effective in another class. For example, Coiffier 1997 describes studies of Grade A-D NHL patients as a grouping of "low-grade" patients. Yet, the reported results show that rituximab treatment of these patients yielded markedly different responses for Grade A patients (11% ORR) as opposed to Grades B-D patients (57%). Ex. 1014, 002; *see also* Ex. 1028, 012 (contrasting positive results with rituximab treatment in low-grade histologies with "less than impressive" "response data in intermediate . . . histologies"). Additionally, studies of rituximab monotherapy in IG- and HG-NHL patients with bulky disease showed a complete lack of response in patients with tumors ≥10 cm in diameter. Ex. 1015, 003 (Table 3). These are further examples consistent with the Board's conclusion in the prior IPR that the LG-NHL patient population is distinct from the IG-NHL patient population. Boehringer Decision at 18, 21.

VI. Ground 2: Link in view of McNeil and the "1997 Rituxan Label"

Petitioner presents this tag-along ground, substituting the "1997 Rituxan Label" to allegedly provide the same disclosures as the "Transcript." But Petitioner also fails to establish that the "Label" is available as a printed publication, as discussed above in Section IV.B. So Ground 2 also fails. Even assuming that the "Label" was a printed publication, the Ground still fails for the same reasons set forth in §§ V.B-V.D.

A. This ground fails because the "Label" is not available as prior art.

The "Label" is the only reference that Petitioner relies upon in Ground 2 as purportedly teaching the treatment of patients with "bulky disease" of any kind. Since it is not available as prior art, the ground fails. *See* § V.A.

B. Ground 2 also fails for the same reasons as Ground 1.

Petitioner's arguments would fail even assuming that the "Label" is available as prior art in this proceeding. Petitioner characterizes the "Label" as "disclos[ing] positive results from the same clinical trial of patients with bulky disease that was discussed in the FDA Transcript." Pet. at 47. Because Petitioner expressly notes that the disclosures of the "Label" are meant as stand-ins for those of the "Transcript" in Ground 1, there is similarly no reason to combine the "Label's" teachings with Link and McNeil. Nor would a POSA have had a reasonable expectation of success in combining the "Label" with Link and McNeil to arrive at the claimed invention. Thus, Patent Owner's arguments with respect to Ground 1, §§ V.B-V.D, are equally applicable here.

C. Any purported differences or additional teachings in the "Label" as compared to the "Transcript" do not cure the failings of Ground 1.

Petitioner relies on the "Label's" disclosure of a study of patients with LG-NHL presenting with bulky disease. The "Label" contains only one indication: "treatment of patients with relapsed or refractory ***low-grade or***

follicular, CD20 positive, B-cell non-Hodgkin's lymphoma." Ex. 1008, 001. Like the "Transcript", the "Label" fails to mention DLCL or any IG-NHL. Even amongst the narrow group of LG-NHL patients tested, the "Label" showed a different response pattern based on the patients' subtype of LG-NHL, with significant differences in response for Grades B-D (ORR 58%) as compared to Grade A (11%). Ex. 1008, 001.

1. The "Label" still only discloses the treatment of patients with LG-NHL.

Only one study on the "Label" discloses the treatment of bulky disease, and it appears to be the same study referenced in the "Transcript." Specifically, the "Label" refers to a study treating twenty-nine patients with "relapsed or refractory, bulky (single lesion of >10 cm in diameter), ***low grade NHL***" with 375 mg/m^2 of Rituxan for four weekly infusions. *Id*. Only 21 of those patients were evaluable for a response, of which only 10 obtained a complete or partial remission. *Id*.

2. The "Label" does not discuss the treatment of elderly patients with bulky disease.

The "Label" contains only one reference to patients aged over 60, but this is in connection with a clinical study separate from the study in which LG-NHL patients with tumors >10 cm were treated. Ex. 1008, 001 (left column). On the other hand, in the "Label" study describing the treatment of low-grade bulky disease patients, no age data is provided. *Id*. (right column).

Thus, because the "Label" (i) addresses only LG-NHL, (ii) fails to identify an elderly patient with bulky disease, and (iii) fails even to indicate the number of elderly patients treated, it does not teach any element of the claimed patient population, failing to cure any of the deficiencies in Link and McNeil.

3. Petitioner fails to explain how a POSA would supposedly apply the teachings of the references to arrive at the claimed invention.

Petitioner also fails to "clearly explain[], or cite[] evidence showing, ***how*** the combination of [] references was supposed to work." *Pers. Web Techs. LLC v. Apple, Inc.*, 848 F.3d 987, 994 (Fed. Cir. 2017). The only administration of rituximab described in the "Label" is described in a dosing schedule that involves ***weekly*** infusions of 375 mg/m^2 for four weeks. This is incompatible with Link, which discloses that patients were given rituximab at a dose of 375 mg/m^2 every three weeks. Thus, the rituximab dosing taught on the "Label" is nearly ***three times higher*** than that suggested in Link, suggesting that the only evidence of successful bulky disease treatment (albeit in LG-NHL) was obtained because of a significantly higher dose and/or dose frequency taught in the "Label" (which is the same in this regard as the "Transcript"). Thus, Petitioner has not shown that the Link regimen, which uses much less frequent rituximab administration in combination with CHOP, would be expected to successfully treat bulky disease in elderly DLCL patients based on the "Label's" dissimilar findings.

Petitioner also fails to articulate how a POSA would have reconciled the "Label's" weekly dose frequency with Link's tri-weekly dose schedule to arrive at the claims. The required detail and explanation simply is absent from Petitioner's papers.

Moreover, Petitioner's proposed combination does not take into consideration whether the "Label's" frequent rituximab infusions would be poorly tolerated by elderly patients. It was well known in the art that elderly NHL patients may have "changes in liver and kidney functions that may alter drug metabolism; moreover, they have a reduced bone marrow reserve," which would lead a POSA away from administering higher and more frequent doses of the B Cell depleting antibody, rituximab. Ex. 2006, 10. Here again, Petitioner simply ignores this teaching.

VII. Ground 3: "E4494 Patient Consent" form in view of the FDA "Transcript"

A. The ground must fail because the "E4494 Consent Form" and FDA "Transcript" are not available as prior art.

Since neither reference cited in the ground is available as prior art, the ground must fail. *See* §§ IV, V.A.

B. The "E4494 Consent Form's" disclosures fail to meet the limitations of the claim, and these deficiencies are not cured by the "Transcript."

1. The only disclosure discussed by Petitioner is the title of the "E4494 Consent Form."

The only disclosure relied upon by Petitioner in the "Patient Consent Form" is the title, a sentence fragment that reads: "Phase III Trial of CHOP and Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients 60 Years or Older with Diffuse Mixed, Diffuse Large Cell and Immunoblastic Large Cell Histology Non-Hodgkin's Lymphoma." Dr. Lossos concedes that neither the consent form nor the associated protocol (which Petitioner does ***not*** cite or utilize in this ground) discloses the treatment of DLCL patients with bulky disease and instead argues that "a POSA would have known that DLCL is often characterized by bulky disease." Ex. 1003, ¶98. But Petitioner cannot establish that the E4494 patient population inherently included bulky disease DLCL patients based on probabilities (at a minimum because the evidence presented does not establish that any bulky disease DLCL patient ever enrolled). *See* § V.B. Yet that is exactly what Petitioner attempts with Dr. Lossos's claim that bulky disease is "often" present.

2. The FDA "Transcript" does not cure the deficiencies of the "E4494 Consent From."

The "Transcript's" deficiencies—namely its limited disclosures regarding only patients with LG-NHL—are addressed in § V.B.2.

C. There is no reason to combine the "E4494 Consent Form" with The "Transcript" with a reasonable expectation of success.

In this Ground, the teachings of the "E4494 Consent Form" stand in for the teachings of Link and McNeil. Just as there is no reason to combine Link and McNeil with the FDA "Transcript" with a reasonable expectation of success in Ground 1, *see* § V.C-V.D, there is also no reason to combine the "E4494 Consent Form" and the "Transcript" with a reasonable expectation of success in this ground.

VIII. Ground 4: Sonneveld in view of Link

Petitioner alleges that Sonneveld taught the treatment of elderly DLCL patients with CHOP, and proposes combining it with Link to arrive at the claimed method. But as in Grounds 1-3, Petitioner still fails even to identify prior art separately teaching all limitations of the claims. It also fails to provide any reason why a POSA would or could have combined Sonneveld and Link to arrive at the claimed invention with a reasonable expectation of success. Institution should therefore be denied on this ground as well.

A. Sonneveld and Link do not teach the Treatment of DLCL Patients with Bulky Disease.

1. Sonneveld does not teach the administration of CHOP to the claimed patient population.

Sonneveld describes a comparative study of CHOP versus CNOP chemotherapy in elderly patients (>60 years old), including patients with

Grades D-H NHL. Ex. 1009, 004. The characteristics of the patients analyzed are reported in Table 1. *Id.* at 005. The Sonneveld study treated 72 patients with CHOP, of which 27 had grade G NHL. *Id*. Of the 72 CHOP patients, 33 were reported to have bulky disease; there is ***no indication*** as to how many, if any, of the DLCL (grade G) patients in the "CHOP group" had bulky disease. *Id*. Further, Sonneveld provides response rates for the study arms (CHOP v. CNOP) generally, but does not break out response rates separately by NHL grade (whether DLCL or otherwise), nor does it break out the response rates for bulky disease patients. *Id.*, Table 2.

Thus, Sonneveld does not identify the treatment of a single elderly DLCL patient with bulky disease—it does not even teach the simple administration of CHOP to such a patient. *See* § V.B (obviousness cannot be established by inherency). Petitioner's suggestion that "Sonneveld explicitly teaches the efficacy of CHOP to treat bulky disease," Pet. at 56, is therefore entirely unfounded. Sonneveld does not even report the response rate for bulky disease patients separately. It is impossible to tell whether Sonneveld's regimen had any beneficial effect in bulky disease patients.

What's more, Petitioner's own expert has discredited data from the Vose study that, as here: (a) notes how many patients have bulky disease and provides overall response rates, but does not discuss how many of those patients had the relevant category of NHL; and (b) notes how many patients

had bulky disease, but does not indicate the response rate for that particular group of patients. Ex. 1003, ¶117, n. 7. Since Sonneveld does not contain data specifically breaking down clinical response rate based on bulky disease status, it provides what Dr. Lossos accurately describes as "insufficient information [that] makes it impossible to determine whether" efficacy or lack thereof was based on other factors. *Id*., ¶121.

Even indulging Petitioner's speculation as to probabilities, at most Sonneveld teaches the administration of CHOP to a total of 11 bulky disease grade G patients (44% of 27 total grade G patients).[9] By Dr. Lossos's admission, such a sample size is too small to draw conclusions of efficacy, particularly since there is no indication given as to how many of the bulky disease patients were successfully treated. *See id.*, ¶121(discrediting portions of Coiffier 1998 because "there are ***only*** 5 patients who had tumor lesions ≥ 10 cm in size in the Coiffier 1998 study—***too few from which to draw a conclusion about efficacy***.").

2. Link does not cure Sonneveld's deficiencies.

Petitioner relies on Link to provide the disclosure of R-CHOP in a younger patient population. *See* § V.B.1(a). Link does not cure Sonneveld's

[9] Of course, this disregards clear Federal Circuit precedent precluding the finding of obviousness based on inherency by probabilities.

failure to teach the claimed population of elderly patients whose DLCL presents with bulky disease. *See id.*

B. Petitioner gives no reason why a POSA would have combined Sonneveld and Link.

Petitioner fails to "articulate a reason *why* the PHOSITA would have been motivated to modify" Sonneveld, which explicitly describes the treatment of elderly patients, with Link, which appears to exclude such patients. *In re Nuvasive*, 842 F.3d 1376, 1384 (Fed. Cir. 2016). In fact, Sonneveld would direct a POSA away from modifying its protocol by utilizing Link's R-CHOP combination therapy because Sonneveld, like McNeil, explicitly points out that elderly patients are studied separately and that patients over 60 years of age "tolerate intensive treatment poorly." Ex. 1009, 003.

Petitioner and Dr. Lossos have not articulated any reason why a POSA would have looked to the Link study, which focuses on a younger population in order to modify the results of Sonneveld's focused, targeted study. *See e.g.*, Ex. 1009, 003-004 (describing study of patients older than 60 years of age and noting that "these patients have been underrepresented [in prior studies] because they tolerate intensive treatment poorly.").

Given that Sonneveld reported positive results, a POSA would not be motivated to "optimize" its intensive treatment regimen by further adding rituximab and reducing the time between chemotherapy cycles as taught in

Link. These are steps the art suggested would likely lead to decreased tolerance of therapy in elderly patients. Nor has Petitioner established that an optimization rationale is applicable here, for the all the reasons addressed in § V.C.2. Indeed, the art-recognized toxicity concerns in elderly patients lead the POSA away from the "optimization" suggested by Petitioner—namely applying Link's R-CHOP combination therapy.

C. A POSA would not have a reasonable expectation of success in combining Sonneveld and Link to treat elderly patients with bulky DLCL.

First, even assuming that Sonneveld teaches the treatment of elderly DLCL patients with bulky disease with CHOP (it does not), adding Link's disclosure of R-CHOP combination therapy would not have given a POSA a reasonable expectation of success in treating those patients. Just as explained in § V.D.1, Petitioner has also failed in this ground to establish the successful treatment of the claimed patient population with R-CHOP.

Moreover, Sonneveld and Link, both separately and in combination, fail to disclose the successful treatment of an elderly DLCL patient with bulky disease. Sonneveld fails to describe the successful treatment of such a patient, expressly or implicitly, and Link adds nothing regarding the treatment of bulky disease. *See* Ex. 1003, ¶117 (study data that fails to disaggregate characteristics for a subpopulation is uninformative). As in the data discredited by Dr. Lossos,

Sonneveld fails to mention any therapeutic success (expected or not) in treating DLCL presenting with bulky disease" in patients >60 years old.

Link does not cure this deficiency, because it mentions neither bulky disease nor elderly patients. In fact, Link treats a population significantly younger than that targeted in the claims. *See* § V.B.1(a). Thus, a POSA would not have applied Link's teachings to the known-to-be-unpredictable elderly patient population with a reasonable expectation of success. *See id.*

IX. 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 '244 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.").

X. CONCLUSION

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

Dated: July 5, 2017

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, the undersigned certifies that on July 5, 2017, a copy of the foregoing document **BIOGEN, INC.'S PATENT OWNER PRELIMINARY RESPONSE** and **Exhibits 2001-2003, and 2006-2009** have been served in its entirety via e-mail, as agreed, on counsel of record for petitioners at the following address:

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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 13,769 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 5, 2017

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