UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.

Petitioner,

v.

BIOGEN, INC.

Patent Owner.

Case IPR2017-01167
U.S. Patent No. 8,557,244

PATENT OWNER'S PRELIMINARY RESPONSE

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I. INTRODUCTION

The Board should decline to institute IPR2017-01167 because Petitioner fails 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 particularly hard-to-treat sub-population of cancer patients: elderly patients with diffuse large cell lymphoma ("DLCL") who further present with large, or "bulky," tumors.[1] DLCL is a particular type of intermediate-grade ("IG") non-Hodgkin's lymphoma ("NHL"). The claimed treatment methods involve combining Patent Owner's therapeutic antibody rituximab with a chemotherapy combination known in the art as "CHOP."[2]

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[1] The claims of the '244 patent define "bulky" tumors or "bulky disease" as a "tumor >10 cm in diameter." Ex. 1001, Claim 1. Unless otherwise noted, references to "bulky disease" in this paper refer to tumors >10 cm in diameter.

[2] CHOP refers to the combination of **C**yclophosphamide, **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.

Before the priority date, those skilled in the art were greatly concerned that CHOP chemotherapy alone was too 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")—of which DLCL is one type—were not promising in general, and were particularly discouraging for patients with bulky IG-NHL tumors. Indeed, studies had shown that rituximab "was insufficient to treat" IG-NHL accompanied by bulky disease. Pet. at 47. 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 bulky IG-NHLs to create a safe and effective treatment for elderly DLCL patients whose disease presents with bulky tumors.

Despite art-recognized toxicity concerns with the use of standard CHOP chemotherapy in elderly patients, the central reference in both of Petitioner's grounds, Shipp (Ex. 1009), doses the known-to-be toxic elements of CHOP chemotherapy at up to ***five times*** the standard dose and reports ***severe, life-threatening*** toxicity in all patients studied. Petitioner and its expert significantly understate this toxicity, describing it only as "'grade 4 hematologic toxicity' (on a scale of one to five, with five being the highest)." Ex. 1002, ¶ 55. Petitioner's papers fail to mention that Grade 4 toxicity is

defined by the National Cancer Institute as toxicity that results in a "life threatening or disabling adverse event" and Grade 5 is death. Ex. 2013, 5.

Shipp also fails to teach the treatment of any DLCL patient greater than 60 years old with bulky disease. As an initial matter, Shipp does not disclose which of its patients had DLCL, as opposed to a different IG-NHL histology (or even a high grade ("HG") NHL histology, as such patients were also included). Moreover, while Petitioner relies on the treatment of four patients aged 60 and above (with some unspecified histology) as corresponding with the claimed patient population, in fact only a single one of those patients had a bulky tumor >10 cm in diameter. But even assuming that the four patients in Shipp upon which Petitioner relies actually satisfied the claim limitations requiring DLCL accompanied by bulky disease >10 cm (they do not), Shipp notes that a four-patient dataset would be too small "to accurately determine response rates." Ex. 1009, 5. Thus a POSA could not conclude from Shipp's data that using high-dose CHOP in elderly patients represented any improvement over conventional therapies for IG-NHL.

This is doubly so in light of prior art, including McNeil (Ex. 1003), which taught that even standard CHOP was thought to be "markedly less successful in older patients" and "more toxic in this age group." Petitioner offers no explanation as to why a POSA would use Shipp's protocol as a

starting point for the treatment of the claimed patients in view of the shortcomings taught by its own evidence and recognized by its expert.

In addition to the aforementioned general toxicity concerns, Shipp further specifically warns the POSA of its concern for—and takes painstaking steps to try to mitigate and monitor—"synergistic cardiotoxicity" (even in younger patients) between the cyclophosphamide and doxorubicin in its regimen. Before the invention of the '244 patent, rituximab also was known to be associated with potential cardiotoxicity. A POSA thus would have been wary of exacerbating this known cardiotoxicity risk by adding rituximab to Shipp's regimen. Yet, despite Shipp's caution, Petitioner is totally silent on the issue, and fails to offer any evidence to explain why a POSA would have believed rituximab could have safely been added to Shipp's regimen, especially for the claimed elderly patients.

Indeed, the lack of any reason to combine Shipp with the other art Petitioner cites is underscored by the fact that Petitioner never is able to articulate a specific combination therapy based on its proposed combinations of references. Petitioner asserts that a POSA would be able to add rituximab to Shipp's regimen to "increase effectiveness, lower toxicity, or accomplish both at the same time." Ex 1002, ¶ 40. But it never explains what a POSA would actually do. Would he reduce the number of cycles of CHOP therapy? If so, by how many? Would he reduce the amount of cyclophosphamide in each cycle

but keep the number of cycles constant? What about the amount of doxorubicin? How much rituximab would be administered? When relative to the CHOP agents? These and myriad other questions unanswered by Petitioner and its expert reveal that, at best, Petitioner's argument amounts to an invitation to experiment, without any guidance from the art as to what should be tried. This type of hindsight reasoning cannot establish a reasonable likelihood that a claim is obvious.

Given the above shortcomings, it is not surprising that the Petition also offers no evidence supporting a reasonable expectation of success in treating the claimed elderly DLCL patients with bulky disease. As noted above, Shipp itself makes clear that its data for at most only four elderly patients (who may not have even had DLCL) is not sufficient to accurately determine a response rate, thus leaving a POSA with no basis to assume Shipp's high-dose regimen would be successful in elderly patients. And Petitioner acknowledges that the prior art taught that "rituximab *monotherapy*—i.e. without other drugs—was insufficient to treat tumors ≥ 10 cm in diameter." Pet. at 47. What Petitioner never explains is why a POSA would expect success from adding rituximab—which was shown to be unsuccessful at treating tumors ≥10 cm—to Shipp's regimen.

This is especially true in light of Petitioner's argument that a POSA would add rituximab in order *reduce* the amount of CHOP administered. Yet

Shipp teaches that to obtain any benefit high doses are needed. And Petitioner acknowledges that other references taught that lower, conventional doses of CHOP are "unlikely" to cure bulky disease patients. Pet. at 2-3. Nothing in the art suggests that either reducing the amount of CHOP or administering rituximab would lead a POSA to expect success in treating the claimed bulky disease patients. To the contrary, the art established that each of these approaches was unsuccessful. Only the work of the inventors, viewed through the lens of hindsight, shows that combining what were essentially failed prior art approaches surprisingly yields a safe and effective therapy for elderly DLCL patients with bulky disease.

In short, the Petition offers no basis for a POSA to have administered the claimed therapy to the claimed patients. And the Petition is virtually silent as to evidence of a reasonable expectation of success. Assembling the elements of the claims by cherry-picking them from disparate references is the essence of impermissible hindsight analysis. But that is all the Petition offers. Institution should be denied.

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 (> 60 years old) 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 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, 004. 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 NHL is unpredictable across subtypes.

"[N]on-Hodgkin's lymphoma has firmly established cellular origin with morphologic subtypes corresponding to various stages of lymphocyte differentiation." Ex. 2004, 2. 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.* There are three other types of IG-NHL: IWF "Group D" (follicular large), "Group E" (diffuse small cleaved), and "Group F" (diffuse mixed). *Id*.

NHL classifications serve two key purposes. First, classifications must define "a ***distinct lymphoma subgroup*** and thus establish a proper diagnosis."[3] Ex. 1012, 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*. at 3. Classifications like the IWF were "readily accepted by clinicians and . . . broadly applied" as of the priority date. *Id.*

A POSA would not have assumed that successful treatment of one grade of lymphoma would translate into successful treatment of a different grade. As Petitioner acknowledges, "[t]he type of lymphoma is 'the major determinant[] for treatment outcome and prognosis' because the different classifications of lymphoma respond differently to chemotherapy." Pet. 8. 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

[3] Unless otherwise noted, emphasis in this paper is added by Patent Owner.

intermediate and aggressive histologies to date have been less impressive." Ex. 2005, 12. The Board previously recognized this principle in *Boehringer Ingelheim Int'l v. Biogen, Inc.*, No. IPR2015-00418, 2015 WL 4467391 (P.T.A.B. July 13, 2015) (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 *10 ("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 *11 (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. 1011, 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") 57%) as compared to Grade A (11%). Ex. 2010, 2. 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. 2011, 4.

C. Overview of Petitioner's Primary Art and the State of the Art

1. Shipp (Ex. 1009)

(a) Shipp does not teach a single patient in the claimed population.

Petitioner claims that "Shipp taught all the elements of claim 1 with the exception of using a monoclonal antibody like rituximab in combination with CHOP therapy." Pet. at 44. But a closer inspection of Shipp's actual disclosures vis-à-vis the '244 patent's claims reveals this to be incorrect.

Petitioner begins by pointing to four patients in the Shipp study who were aged 60 or older. Pet. at 38-39. But Shipp does not identify which NHL histology any of those four patients had. *See* Ex. 1002 at ¶ 52 ("Shipp does not say whether these elderly patients had 'diffuse mixed,' 'diffuse large cell,' or 'immunoblastic large cell' lymphoma[.]").[4] Thus, one has no idea from reading Shipp whether any of the four elderly patients actually had DLCL.

[4] Of these various potential histologies, only DLCL is within the claims. Patent Owner disavowed histologies other than DLCL during prosecution. *See* Ex. 1020 at 4-5 (noting that the language of the claims "is limited to patients

Remarkably, Dr. Ozer tries to turn Shipp's silence regarding DLCL into an affirmative disclosure, asserting that "the very fact that Shipp does not distinguish among [types F, G, and H] reflects the understanding of those in the art that there were no significant distinctions in treating" different lymphoma subtypes. *Id*. But such an understanding is refuted by the Petitioner's own admissions, as well as by the prior art and the Board's Boehringer Decision. *See* Pet. at 8 ("[D]ifferent classifications of lymphoma respond differently to chemotherapy."); Ex. 1011, 2 ("histology [*i.e.*, grade] and stage still comprise the major determinants of therapy."); Boehringer Decision at *10, 11 (emphasizing distinctions between different NHL histologies). In short, there is no evidence that Shipp actually tested its regimen on even one elderly DLCL patient, much less evidence of success in treating a patient within the scope of the claims.

Dr. Ozer further states that "Shipp even successfully treated at least three of four patients 60 years or older with intermediate-grade NHL and bulky

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with diffuse large cell lymphoma."). Moreover, immunoblastic large cell lymphoma is not even an IG-NHL; it is an HG-NHL. *See, e.g.,* Ex. 1011, 2 (Table 1).

disease.[5] [Ex. 1009], 3, Table 1, and 6, Table 6." Ex. 1002, ¶76. Dr. Ozer's conclusion that Shipp's regimen taught the successful treatment of elderly patients with bulky disease on the ground that "[o]ne such patient was assigned to group one, one to group two, and two to group three," and "[w]ithin these groups, only one patient in group three had no response to therapy" is unsupported by the record. *Id.* at ¶51.[6] As noted above, there is no evidence that any of those four patients was a DLCL patient. Likewise, only one of those patients had a tumor >10 cm. *See* n.5. But even assuming, contrary to the evidence, that these four elderly patients somehow corresponded the claimed patient population, Shipp itself notes that four patients is too small a sample "to accurately determine response rates" and support conclusions about efficacy. Ex. 1009, 5. Dr. Ozer never explains how a POSA could conclude from tests

[5] In fact, only Shipp's patient 6 was >60 years old and had a tumor greater than 10 cm in diameter (as required by the claims). Like all of the patients in Shipp, the type of NHL from which patient 6 suffered was not disclosed.

[6] In addition, one patient in group three responded but died because of toxicity, Ex. 1009, 5, and another patient in group three did not respond to therapy. *Id.*, Table 6. Petitioner has not established that these were not patients 11 and 14, the patients in that group over age 60.

on four patients that there was a favorable response rate when Shipp's authors themselves reported that four patients was too few from which to draw any accurate conclusions about efficacy or improvement over conventional therapy. Accordingly, a POSA reading Shipp could not conclude that its regimen was successful with any elderly patients, much less DLCL patients in particular, and thus would not be motivated to use this treatment in the claimed patient population.

And contrary to Dr. Ozer's assertion, one cannot discern from Shipp whether any of these four elderly patients even had "intermediate-grade NHL." Shipp's patients included those with "large-cell immunoblastic lymphoma," which is a HG-NHL. Ex. 1009, 2. Table 1 does not identify the patients' histology (whether DLCL or otherwise). Thus, there is no support in Shipp for Dr. Ozer's assertion that the four elderly bulky disease patients disclosed had "intermediate-grade NHL" (let alone DLCL) given that the study population also included patients with HG-NHL. In sum, Shipp provides no evidence of efficacy in either elderly patients or in DLCL patients, much less in elderly DLCL patients with bulky disease >10 cm in diameter, as required by the claims.

(b) Shipp's regimen caused life-threatening adverse reactions.

Shipp's high-dose regimen caused all patients in the study to experience life-threatening toxicity, and thus would not have been seen as clinically acceptable. Petitioner and Dr. Ozer minimize the severity of adverse events resulting from such toxicity, describing them as only as "Grade 4" toxicity and noting that the Grades are "on a scale of one to five, with five being highest." Ex. 1002, ¶ 55. Petitioner fails to mention that Grade 4 toxicity is defined by the National Cancer Institute as a "life threatening or disabling adverse event" and Grade 5 is death. *See* Ex. 2013 at 5.

(c) All of Shipp's disclosures relate to high-dose CHOP.

Petitioner's expert asserts that "Shipp taught that CHOP therapy is an effective regimen for intermediate- and high-grade NHL (i.e., DLCL) accompanied by bulky disease (i.e., tumor >10 cm in diameter). Ex. 1009, 1." Ex. 1002, ¶76. This statement, in a one-paragraph subpart of his declaration that does not refer to his other discussion of Shipp, ignores that Shipp at most teaches that its ***high-dose*** CHOP regimen had some purportedly successful results (albeit with significant side effects) in younger patients of various unspecified IG- and HG- histologies. Ex. 1009, 2; Ex. 1002, ¶ 48 ("[Shipp] analyzed the effectiveness of ***high-dose*** CHOP . . . ."). Nothing in Shipp suggests lower doses of CHOP could be effective for any bulky disease

patients. *See* Pet. at 2 (describing patients with bulky disease as having a "higher risk of failure" with standard CHOP).

In his discussion of Shipp, Dr. Ozer further states that "CHOP therapy, when used alone, can treat DLCL accompanied by bulky disease using standard-dose CHOP therapy or high-dose CHOP therapy." Ex. 1002, ¶76. But Shipp teaches only high-dose CHOP therapy. Neither Shipp, nor any other document cited by Dr. Ozer, supports the assertion that standard-dose CHOP therapy is effective to treat DLCL accompanied by bulky disease. Indeed, Petitioner admits the opposite in its petition, noting that bulky disease patients are "'unlikely to be cured with standard therapy' (e.g., with standard doses of CHOP)." Pet. at 2-3. The absence of any such evidence of efficacy with lower doses of CHOP is a key omission, as discussed below (*see* IV.D.2), because Shipp is the only reference reporting any response (albeit with serious and sometimes fatal side effects) in bulky tumors of any histology, and Shipp exclusively used high-dose CHOP regimens to do so.

2. Link (Ex. 1005)

(a) Link does not disclose a single patient older than 60 or with bulky disease.

Link is an abstract describing a pilot study of patients with IG- or HG-NHL treated with R-CHOP. Ex. 1005, 5. Of the 31 patients studied, 21 had DLCL (Grade "G" NHL), as opposed to other histologically different subtypes.

Id. Although Link states that the median patient age for this mixed population was 49 years old, Link does not identify a patient (with DLCL or otherwise) that was over 60 years old. Link also does not disclose any patient (with DLCL or otherwise) with a tumor >10 cm in diameter. Thus, Link is uninformative as to how patients with DLCL presenting with bulky disease would respond to its treatment regimen.

(b) Link does not suggest that rituximab would be safe or effective if used with Shipp's high-dose CHOP regimen.

In contrast to Shipp's high-dose CHOP regimen, Link discloses a possible combination therapy of rituximab with standard-dose CHOP, in which the cyclophosphamide dose is 750 mg/m^2 (20-25% of the dose used in Shipp), and doxorubicin is dosed at 50 mg/m^2 (~50% of the dose used in most of Shipp's dosing schemes). Ex. 1005, 5. Petitioner's assertion that Link "teach[es] that the addition of rituximab adds efficacy but not toxicity" to standard CHOP, Pet. at 35, is unsupported. Link's protocol did not include a control group of patients treated with CHOP alone. Nor does Link provide a baseline response rate for standard CHOP to which its R-CHOP response rates could be compared. Link does not even make the claim Petitioner asserts it does; it merely notes that its regimen "***may*** offer higher response rates." Ex. 1005, 5.

And in fact Link teaches considerable toxicity associated with its regimen, including Grade 4 neutropenia in 13/31 patients, as well as numerous additional Grade 3 toxic events. *Id*. One cannot extrapolate from Link's study of ***standard*** CHOP that adding rituximab to the already extremely toxic Shipp high-dose regimen would result in tolerable toxicity, let alone that the combination would not result in increased toxicity.

3. Coiffier (Ex. 1006)

Petitioner relies on Coiffier as purportedly teaching the administration of rituximab to treat intermediate grade NHL. Pet. at 45. Petitioner also admits that "Coiffier taught that rituximab *monotherapy*—i.e., without other drugs—was insufficient to treat tumors ≥10 cm in diameter." Pet. at 47. Indeed, Coiffier taught that responses to rituximab decreased as tumor size increased, and that while "patients whose largest tumor was less than 5 cm in diameter were more likely to respond (46%) than patients whose largest tumor was greater than 5 cm (17%)[, ***n]o responses were observed in patients whose largest tumor was greater than 10 cm in diameter***." Ex. 1006, 4. Coiffier thus taught that rituximab monotherapy was ineffective at treating bulky disease as the term is used in the claims.

Further, for both the bulky disease (≥10 cm) patients, as well as the patients with tumors between 5 and 10 cm, Coiffier does not provide information regarding the patients' ages or NHL histology. Thus, it is unclear

whether any of those patients were elderly NHL patients, let alone elderly DLCL patients (as opposed to one of the other histologies studied).

4. McNeil (Ex. 1003)

McNeil is a news article from the Journal of the National Cancer Institute that shows, consistent with other art, that POSAs before the priority date were concerned with CHOP's toxicity in elderly IG-NHL patients. At that time, POSAs 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. 1010, 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. 1003, 1 ("CHOP … is more toxic in this age group.").

Petitioner's evidence further notes that in 1997 elderly patients were known to "have changes in liver and kidney functions that may alter drug metabolism; moreover, they have a reduced bone marrow reserve and may have metabolic and cardiovascular diseases." Ex. 1010, 10. "As a consequence, ***because toxicity may be enhanced, many physicians believe that elderly***

patients are unable to withstand intensive chemotherapy." *Id*. Due to the worse prognoses for elderly patients with DLCL, physicians attempted to devise treatment regimens "in which different chemotherapeutic agents are chosen, and drug doses are reduced or scheduled less frequently." Ex. 2009, 3. However, these regimens had been found to "produce results inferior to those achieved with the standard combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), or a comparable regimen that substitutes pirarubicin for doxorubicin." *Id*. This is consistent with McNeil's finding that "[o]ne reason for poorer outcomes in older patients is thought to be" that such patients often can "take three or four treatments, but they have a hard time getting" to the standard six to eight. Ex. 1003, 1. McNeil directed away from using high-dose CHOP in the elderly, noting a desire for "CHOP ***alternatives*** [that] could also turn out to be ***less toxic*** chemotherapy regimens…[for] the elderly." Ex. 1003, 2. McNeil also suggested reducing the amount of CHOP given to elderly patients, stating "another strategy is the use of ***fewer doses*** of CHOP in elderly patients who cannot tolerate the full regimen." Ex. 1003, 2. In light of McNeil, a POSA would not be inclined to give an elderly patient high-dose CHOP.

5. Efforts to increase CHOP doses in elderly patients failed, even with biologic support.

The standard CHOP regimen dosed cyclophosphamide at 750 mg/m^2, doxorubicin at 50 mg/m^2, vincristine at 1.4 mg/m^2, and prednisone at 100 mg/day for 5 days for at least 6 cycles, as described in Meyer. Ex. 2009, 4. This standard dosage scheme was used in Link. *See* Ex. 1005, 5.

Because of toxicity concerns associated with CHOP therapy, even at standard dose levels, POSAs were exploring means of reducing its toxic effects before the priority date. One approach, described in Meyer, was to co-administer the biologic G-CSF (filigrastim) as additional support to mitigate toxicity. Ex. 2009, 2-3. At the same time, POSAs were also attempting to increase the doses of the components within CHOP in an effort to increase efficacy. *Id*. But while Meyer reported that "standard CHOP [dosages] with G-CSF can be safely given to elderly patients[, e]scalating the dose of cyclophosphamide within CHOP to 900 mg/m^2 [*i.e.* 1.2 times the normal dose] for 6 treatment cycles does not appear to be feasible even with G-CSF [support]." *Id* at 1-2.

6. Rituximab monotherapy was ineffective in treating IG-NHL accompanied by bulky disease (tumor ≥10 cm).

Before the priority date, although 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. 2005, 12 (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 ≥10 cm in diameter, 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. 1006, 3, Table 3 (reporting 0% response rate in all patients with IG-NHL tumors ≥ 10 cm in diameter). Petitioner even admits as much, noting that "Coiffier taught that rituximab *monotherapy*—i.e., without other drugs—was insufficient to treat tumors ≥10 cm in diameter." Pet. at 47.

III. THE CLAIMS ARE DIRECTED TO "DIFFUSE LARGE CELL LYMPHOMA."

While Petitioner states that the claims should be given "their plain and ordinary meaning," Pet. at 26, its analysis of proposed grounds for trial suggests that it did not apply that plain and ordinary meaning in the substantive portion of its papers. Specifically, Petitioner's reliance on Shipp's disclosure of a mixed and nonspecific group of NHL histologies suggests that Petitioner has applied an interpretation of "diffuse large cell lymphoma" that is inconsistent with that term's ordinary meaning to a POSA, particularly as understood in the context of 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) (quotation marks 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 plain and ordinary meaning of "diffuse large cell lymphoma" does not include "diffuse mixed cell lymphoma" (IG-NHL of IWF Grade F) and "immunoblastic lymphoma" (IG-NHL of IWF Grade H), which are different diseases. *See* Ex. 1011, 2 (Table 1). Petitioner's tacit suggestion to the contrary, *see, e.g.*, Ex. 1002, ¶ 52, treating these different diseases as satisfying the claim limitation, should be rejected.

A POSA reviewing the claims in light of the specification would have understood 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").

A different construction also would conflict 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. 1020, 5. In light of this clear disavowal of NHLs other than DLCL, Petitioner's implied construction, which includes IG-NHL of Grade F histology and HG-NHL of Grade H histology (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), diffuse large cleaved cell (DL-C), diffuse noncleaved large cell (DL), [and]

immunoblastic large cell (IBL)." *See* Ex. 2012, 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").

IV. GROUND I: SHIPP AND LINK IN VIEW OF MCNEIL

Ground I relies on Shipp and Link as purportedly disclosing various individual claim limitations, and relies on McNeil as allegedly providing motivation that would have given a POSA a reason to combine the two references to arrive at the claimed invention. Ground I fails.

A POSA as of the priority date would not have elected to use the Shipp regimen as a starting point for combination therapy in light of its expected and reported Grade 4 life-threatening toxicity. *See* § II.C.1; Ex. 1002, ¶ 55; Ex. 2009, 6-7 (explaining that their dose escalation study did not escalate cyclophosphamide dosages within CHOP above 900 mg/m^2 because "one patient died of overwhelming sepsis after receiving three cycles; three patients declined further therapy after three, four, and five cycles respectively because of fatigue and weakness felt to be secondary to cumulative treatment toxicity; and, one patient was taken off of treatment after five cycles because of pneumonitis of uncertain etiology. Of the three patients who declined further

therapy because of cumulative toxicity, two had been previously hospitalized for treatments of infections.").

Far from providing a suggestion to follow Shipp and then further modify its teachings by adding rituximab, McNeil emphasizes the significant toxicity concerns a POSA would have had about using even standard doses of CHOP in elderly patients. Ex. 1003, 1 ("CHOP . . . is more toxic in this age group."). Link also does not cure Shipp's deficiencies because it does not address the claimed patient population, and represents an approach that is incompatible with Shipp due to its substantially different dosage scheme and administration schedule. Accordingly, Petitioner fails to establish that there would have been a reason to combine the disparate teachings of the cited references and that there would have been a reasonable expectation of success in doing so.

A. Purported "Applicant Admitted Prior Art" is not entitled to any consideration in this Ground.

As an initial matter, Ground I refers to purported "Applicant Admitted Prior Art" ("AAPA"). But Petitioner's identification of challenge pursuant to 37 C.F.R. §§ 42.104(b) and 42.22(a)(1) fails to identify this purported AAPA as a basis for the challenge of Ground I (or any other ground). Pet. at 6. Petitioner nevertheless attempts to bolster Ground I by quoting extensive portions of the '244 patent's specification as purportedly amounting to "AAPA" conceding "that chemotherapy was already used in the prior art to

treat patients with DLCL accompanied with bulky disease." Pet. at 37. The Board should accord no weight to this alleged AAPA for at least three reasons.

First, in attempting to define the alleged admission, Petitioner mischaracterizes the content of the specification. Petitioner asserts that the "Background of the Invention" supports finding that "traditional chemotherapy such as CHOP was a 'conventional therapy,' i.e., a part of the prior art, for '[i]ntermediate- and high-grade lymphomas . . . often characterized by large extranodal bulky tumors.' [Ex. 1001] at 1:33-34." Pet. at 36-37. But the specification does not suggest, as implied by Petitioner's assertion, that POSAs or the inventors considered CHOP as a "traditional chemotherapy" or a "conventional therapy" for DLCL. Although the "Background of the Invention" mentions "conventional" chemotherapy, CHOP chemotherapy is not mentioned until the "Detailed Description of the ***Invention.***" *Cf.* Ex. 1001 1:20-2:2; 3:27-34. Likewise, Petitioner also draws its conclusion that "'diffuse large cell lymphoma' is an intermediate-grade lymphoma. *Id*. at 2:42-45," Pet. at 37, from the "Detailed Description of the Invention" section. These are significant errors because even if the "Background" section were AAPA (it is not), the discussion in the "Detailed Description of the ***Invention***" is not.

Second, even if there were any admission, AAPA is not a prior art patent or printed publication within the meaning of § 102(b) and thus cannot be used a basis upon which to cancel claims in this IPR. *LG Elecs. Inc. v. Core Wireless*

Licensing S.A.R.L., No. IPR2015-01987, Paper No. 7 at 18 (P.T.A.B. Mar. 24, 2016) (IPR challenge based on AAPA "does not identify any patents or printed publications, [and thus] fails to comply with Section 311(b) or Rule 42.104(b)(4)."); *Kingbright Elecs. Co. v. Cree, Inc.*, No. IPR2015-00741, 2015 WL 5028023, at *4 (P.T.A.B. Aug. 20, 2015) ("[W]e reject Petitioner's asserted ground relying solely on [] alleged 'AAPA' ***as not based on a prior art patent or printed publication***.");[7] *See also* 35 U.S.C. § 311(b).

Petitioner's citation to *Ex parte Xintian E. Lin & Qinghua Li*, No. 2015-7034, 2016 WL 6560248, at *1 (P.T.A.B. Nov. 2, 2016) in support of its AAPA argument, does not help it here. *Ex parte Lin & Li* was an *ex parte* appeal and thus did not (and could not) address the question of whether alleged AAPA can override statutory limitations on the Board's jurisdiction to consider

[7] Of course, the specification of the '244 patent was not publicly accessible before the priority date and therefore cannot be considered "prior art" in any event. Nor do the purported admissions "identify any specific portions of [any] documents mentioned in the cited section of the ['244] Patent as a basis for any asserted grounds of unpatentability," that Petitioner contends constitute, "or otherwise evidence[], a prior art patent or printed publication." *Kingbright* 2015 WL 5028023, at *4.

materials other than patents and printed publications in IPR proceedings.[8] *See* 35 U.S.C. § 311(b); *Kingbright,* 2015 WL 5028023, at *4. Petitioner offers no authority suggesting AAPA can be used at all in an IPR, much less any sound basis to disregard section 311(b) and the Board's holdings in *Kingbright* and *LG Electronics.*

Finally, even if the purported "AAPA" could properly be considered in analyzing this Ground, the cited portions of the "Background of the Invention" fail to mention (i) CHOP; (ii) rituximab; (iii) DLCL; (iv) elderly patients; and (v) bulky disease. Thus, the purported "AAPA" would fail to cure the other deficiencies of the ground even if it were considered.[9]

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[8] Notably, in *Ex Parte Lin & Li*, the applicant "d[id] not dispute [the] explanation" that there was AAPA. 2016 WL 6560248, at *2.

[9] In any event, Petitioner offers no explanation as to how a POSA would apply the purported AAPA to the teachings of Shipp and Link to render the claims obvious; Petitioner makes no effort to link the "AAPA" and the cited art. In fact, Petitioner appears to disclaim reliance on the "AAPA" immediately after introducing it. *See* Pet. at 38 ("***Putting aside these concessions by the applicants***, the prior art itself disclosed the use of CHOP chemotherapy to DLCL patients with bulky disease.").

B. The combination of Shipp and Link fails to disclose the treatment of any elderly patient with DLCL presenting as bulky disease.

As discussed in §§ II.C.1-II.C.2, above, Shipp and Link fail to disclose the treatment of the claimed elderly DLCL patients whose disease presents with tumors >10 cm in diameter. Such patients are simply absent from Petitioner's proposed combination. McNeil, which Petitioner relies on for "motivation to combine," Pet. at 41, does not cure these deficiencies.

C. There is no reason for a POSA to have combined the cited references.

Petitioner offers a hodge-podge of alleged reasons why a POSA allegedly would have combined Shipp and Link to purportedly obtain the claimed invention. None withstand scrutiny.

1. There is no support for Petitioner's assertion that a POSA could modulate the balance of efficacy and toxicity in the claimed patients by adding rituximab to Shipp's regimen.

Petitioner initially suggests that the claimed methods were "obvious to try" as ways to balance the competing concerns of "efficacy and toxicity" in the treatment of the claimed patients. Pet. at 43. Petitioner suggests that a POSA might achieve this goal either by replacing some of Shipp's CHOP doses with rituximab to reduce toxicity, or alternatively by simply adding rituximab to Shipp's regimen without additional toxicity. *See, e.g.*, Pet. at 41. Neither rationale finds support in the art.

(a) The art does not suggest swapping chemotherapy doses for rituximab to reduce toxicity.

Petitioner first suggests that "rituximab could replace some of the CHOP doses in elderly patients and thus reduce toxicity." Pet. at 42. But this is just speculation that is not grounded in the teachings or suggestions of the cited references. Moreover, it is unclear if Petitioner is suggesting replacing a portion of each of Shipp's CHOP doses with rituximab (*e.g.* administer rituximab and cut the amount of CHOP given by some unspecified amount), or if Petitioner proposes giving some unspecified amount of rituximab in lieu of some unspecified number of CHOP cycles. Under either interpretation, nothing in the art suggests that it was within the knowledge of a POSA to obtain efficacy by swapping a portion of a chemotherapy dose with rituximab. Petitioner cites the Ozer declaration, Ex. 1002 at ¶¶ 56-58, in support of this assertion. But the Ozer declaration nowhere states that "rituximab could replace" CHOP doses pursuant to Petitioner's proposal. Pet. at 42. Rather, Dr. Ozer states only that "skilled artisans in the field were still searching for combination therapies that could increase effectiveness, lower toxicity, or accomplish both at the same time." Ex. 1002 at ¶ 56. However, identifying the goal does not make its solution obvious. *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008). Petitioner's proposed modifications to Shipp are not even hinted at in the art. Nothing in Link or McNeil (or any other reference

cited by Petitioner) suggests that rituximab could have replaced some of Shipp's CHOP doses while preserving its alleged efficacy and simultaneously reducing toxicity.

This is particularly so given that whatever "success" Shipp may have achieved, Shipp is emphatic that such "success" is the result of its "high-dose CHOP regimen." *See* Ex. 1009, 1 (abstract). Thus, a POSA would not have been motivated to reduce Shipp's doses of cyclophosphamide and doxorubicin (whether by reducing the number of cycles of CHOP or by reducing the dose per cycle). A POSA would have understood that doing so would destroy the regimen's principle of operation, negating any motivation to make Petitioner's proposed combination. *Plas-Pak Indus., Inc. v. Sulzer Mixpac AG*, 600 F. App'x 755, 759 (Fed. Cir. 2015) ("[A] change in a reference's 'principle of operation' is unlikely to motivate a person of ordinary skill to pursue a combination with that reference."); *see also In re Ratti*, 270 F.2d 810, 813 (C.C.P.A. 1959) (A proposed obviousness combination is inappropriate where the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown . . . , as well as a change in the basic principles under which the [primary reference] was designed to operate.").

Shipp's disclosures also undercut Petitioner's speculation regarding the use of biologic agents to reduce the toxicity associated with CHOP

chemotherapy. Shipp used a biologic, G-CSF, in all of its dosing schemes in an attempt to limit toxicity. But Shipp was unsuccessful in reducing toxicity to an acceptable level, as all patients suffered from Grade 4, life-threatening, adverse events. Given that failure, there would have been no reason to try rituximab—a different biologic for which the cited art did not recognize any toxicity-reducing effect. Petitioner's first rationale is driven entirely by hindsight.

(b) The art does not teach that rituximab increased the efficacy of known chemotherapy regimens.

Petitioner further suggests that adding rituximab could "simply increase the efficacy of existing CHOP regimens [specifically, Shipp] without any added toxicity." Pet. at 42. Nothing in the art suggested that a POSA could add rituximab to a high-dose CHOP regimen (already known to cause Grade 4 adverse events) to achieve what Petitioner refers to as "increased efficacy without added toxicity." Pet. at 42. Petitioner offers no evidence regarding rituximab's ability to increase efficacy when used in combination with high-dose CHOP. Indeed, Coiffier taught that rituximab was ineffective in treating bulky tumors. *See* § II.C.3. Petitioner's suggestion that Shipp's efficacy would be increased by adding an agent demonstrated in the prior art to be ineffective in treating bulky disease is pure speculation. Moreover, as discussed below in § IV.C.2, concerns about overlapping cardiac toxicity between rituximab and

Shipp's high-dose CHOP regimen would have directed a POSA away from adding rituximab to Shipp's already highly-toxic regimen.

Accordingly, the inventors' choice to combine rituximab and CHOP in the claimed patient population was not simply the selection of known approaches from a finite list of predictable solutions to balance "efficacy and toxicity" and achieve a successful treatment for the claimed patients. Nothing in the art suggested the claimed approach. The art in fact taught unpredictability and expressed concern in treating elderly patients using the individual components of the claimed combination therapy, as discussed above. Only with the benefit of Applicant's invention is Petitioner able to piece through the prior art to purport to have identified the claimed therapies. *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 only guidance in the art is at most an invitation to experiment).

2. POSAs would not have combined high-dose CHOP with rituximab given that both therapies individually carried significant toxicity risks in elderly patients.

Even in standard CHOP therapy using normal doses of cyclophosphamide and doxorubicin, POSAs were especially concerned that CHOP therapy was ***unduly toxic*** when used to treat elderly patients with IG-NHL. *See* § II.C.4. Moreover, the drugs used in Shipp's high-dose CHOP were known to carry with them significant risks of cardiac toxicity. For example,

before the priority date, POSAs were concerned with the potential ability of chemotherapy drugs, including cyclophosphamide, to "induce or exacerbate heart failure." Ex. 2015 1, 2-3. The art contained numerous reports on both "reversible and irreversible heart failure[,] indicat[ing] a wide spectrum of cyclophosphamide-induced cardiotoxicity." *Id*., 3. Such cardiotoxicity was also known to be influenced by the patients' condition, dosage, as well as coadministration with other chemotherapies. *Id*. Similarly, elderly patients were known to be at risk of developing "congestive heart failure after low doses of doxorubicin," a risk which could be escalated by "exposure to other cardiotoxic agents." Ex. 2016, 4. Indeed, the art even reported that "life-threatening cardiac failure may occur after conventional 'safe' doses of doxorubicin." *Id*. at 4-5.

The researchers behind the Shipp study appear to have been well aware of these risks. They administered cyclophosphamide "in divided bolus doses on days 1 and 2, and doxorubicin was administered as a 48-hour continuous infusion on days 1 and 2 to minimize the risk of ***synergistic cardiotoxicity***." Ex. 1009, 2. Shipp thus expressly warns a POSA of the risk of cardiotoxicity.

Before the priority date, POSAs also knew that rituximab was associated with cardiac hypotension and arrhythmia. *See* Ex. 2017 at 4. In light of knowledge in the art that cyclophosphamide and doxorubicin were cardiotoxic—perhaps more so in elderly patients (>60 years old) and especially

at high doses—a POSA would not have been inclined to add rituximab to the Shipp regimen for which cardiotoxicity was already an express concern. A POSA would have had significant concerns that combining the two therapies would harm patients, the opposite of a suggestion to combine.

3. Rather than provide a reason to combine Shipp and Link, McNeil actually directs the POSA towards approaches other than severely-toxic high-dose CHOP.

Contrary to Petitioner's suggestions, McNeil does not encourage a POSA to combine the teachings of Shipp and Link to arrive at the claimed combination of rituximab and CHOP in the claimed population of elderly patients whose DLCL presents with bulky disease. McNeil explicitly states that with respect to ***standard*** (i.e., not high-dose) chemotherapy, "[o]lder patients with good performance status can quite often take three or four treatments, but they have a hard time getting to six or eight [the standard number]." Ex. 1003, 1. Given that ***a single cycle*** of Shipp's regimen delivered the same amount of cytotoxic agents as five cycles of conventional regimens, it would have been unlikely for a POSA to select Shipp's high-dose regimen as a starting point in view of McNeil.

Instead of encouraging the combination Petitioner suggests, McNeil in fact directs away from combining Shipp and Link. A POSA would not "look past [McNeil's] warning regarding" elderly patients' inability to tolerate six to eight doses of CHOP because McNeil "expresses concern for failure" due to

toxicity risks. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009).

Moreover, McNeil teaches that part of the reason for the lower efficacy of CHOP in older patients is that it is not tolerated as well, and may be more toxic. Ex. 1003, 1; s*ee also* Ex. 1010, 10 (explaining that in elderly NHL patients, "toxicity may be enhanced, [and] many physicians believe that elderly patients are unable to withstand intensive chemotherapy."). In light of these express teachings that elderly patients cannot endure a full course of six doses of CHOP alone—at normal doses[10]—a POSA would not have combined Shipp's high-dose regimen with the teachings of Link. In fact, Link taught that nearly half of its patients suffered from Grade 4 toxicity (neutropenia), and also reported numerous Grade 3 toxicity related adverse events. Ex. 1005, 5. Given that Shipp considered Grade 4 toxicity, as well as most Grade 3 toxicity (other than nausea/vomiting/diarrhea, alopecia, pain, or hematological toxicity) to be

[10] The Meyer study suggested that with G-CSF support, standard CHOP may be feasibly given in elderly patients "with acceptable toxicity." Ex. 2009, 9. But Meyer does not address elderly patients with bulky disease. This further underscores the fact that a POSA would have no reason to use the claimed combination in the claimed patient population, much less have any reasonable expectation of success.

"dose-limiting," Ex. 1009, 3, Link—given its reported Grade 3 and 4 toxic events—would direct a POSA away from Petitioner's proposed combination therapy, which would include higher doses of CHOP than Link alone.

Though Petitioner never defines its proposed combination, its reliance on Shipp as a starting point further suggests that its proposal relies on higher than standard CHOP dosages. Such therapy would be too toxic in elderly patients. *See* Ex. 2009, 2-3 (concluding, specifically in the context of treating elderly patients with aggressive NHLs, that "[e]scalating the dose of cyclophosphamide within CHOP to 900 mg/m^2 for 6 treatment cycles does not appear to be feasible even with G-CSF.").

Further, according to McNeil, elderly patients "do not maintain remissions as long as younger people," and "have a higher relapse rate, . . . and we don't really understand why." Ex. 1003, 2. As a result, researchers were "always looking for something better." *Id*. (quoting Julie Vose, M.D.). But "knowledge of the goal does not render its achievement obvious," *Abbott Labs.*, 544 F.3d at 1352, and Link does not help bridge the gap between Shipp and the claims. Not only does Link teach the treatment of a population of NHL patients different from the elderly patients discussed in McNeil and in the claims (median age 49 and without bulky disease >10 cm), it relies exclusively and explicitly on six cycles of (standard) CHOP ***plus*** rituximab. Ex. 1005, 5.

4. Petitioner's suggestion that a POSA would have tried rituximab and CHOP as a combination therapy in order to "improve patient compliance" is meritless.

Citing *Allergan, Inc. v. Sandoz, Inc.*, 726 F.3d 1286, 1289-90 (Fed. Cir. 2013), Petitioner also appears to suggest that a POSA would have had a "clear motivation to combine" rituximab and CHOP "into a single formulation to improve patient compliance." Pet. at 42. *Allergan's* rationale—addressing patient compliance for self-administered medication—is inapplicable here because the drugs at issue (*i.e.* chemotherapy and rituximab for treatment of cancer) are administered in a hospital or oncology clinic setting.

Unlike the present case, in *Allergan*, each drug in the proposed combination (a fixed-formulation eye drop) was already independently FDA approved for the treatment of glaucoma or ocular hypertension. *Allergan*, 725 F.3d at 1291. "Moreover, it was common at the time of the invention to provide [the drugs at issue,] brimonidine and timolol[,] to a patient in serial fashion and [the prior art reference] taught that by combining drugs in a fixed-combination formulation, patient compliance could be increased." *Id*. at 1292.

Petitioner has not established a factual basis sufficient to render *Allergan's* compliance rationale applicable to Petitioner's suggestion to add rituximab to Shipp's CHOP regimen. First, unlike *Allergan*, the art does not teach the individual success of either CHOP or rituximab in the claimed patients. Just the opposite, it suggested failure—hardly a reason to combine.

See § II.C.5-II.C.6. Because there was no individual success in the claimed patient population, the art similarly does not teach the serial use of CHOP and rituximab, thus negating any purported rationale under *Allergan* to administer them together. Moreover, as noted in Section IV.C.2 above, toxicity concerns would have directed a POSA away from adding rituximab to Shipp's regimen. It hardly serves patient convenience to combine therapies in a manner that could be toxic to the patient. In short, a "patient compliance" rationale is just circular reasoning here—dosing convenience offers no basis to combine drugs in the absence of evidence that a physician would have a clinical reason to administer that combination in the first place.

Further, CHOP itself contains multiple drugs. The Shipp regimen, administered in a hospital or oncology clinic, required the administration of more than five different drugs (each component of CHOP, G-CSF, and other supporting drugs including mesna and prophylactic antibiotics) over a course of three weeks, by infusion. *See* Ex. 1009, 2, Fig. 1. The cyclophosphamide was given in separate doses on days 1 and 2, and the doxorubicin was "given as a continuous infusion over 48 hours on days 1 through 2." *Id.*, 2. Because such drugs are being administered by infusion or intravenous push in a hospital or oncology clinic setting by medical professionals, compliance, which is a function of the patient's actions, is irrelevant as a motivation to combine. For example, the Shipp regimen included at least a 2-day hospital or clinic stay,

given that it required the administration of doxorubicin "as a 48-hour continuous infusion on days 1 and 2 to minimize the risk of synergistic cardiotoxicity" with cyclophosphamide. *Id*. Shipp teaches that the timing and infusion rate of these drugs must be actively managed by physicians in order to avoid serious adverse reactions; one cannot simply mix together all the drugs and inject them as a common formulation. In any event, given the other drugs administered over the 21 day period, Shipp's regimen likely required a longer hospital stay, or at least routine oncology clinic visits. *See, e.g.*, *id*. Petitioner offers no explanation or evidence as to how patient compliance plays any role in Shipp's protocol, much less how that would differ (if at all) if another drug was included in the already lengthy and complex infusion protocol.

5. Petitioner fails to establish that a POSA would have combined rituximab and CHOP in the claimed patients to leverage purportedly different "mechanisms of action."

Finally, Petitioner asserts that "it was obvious to combine rituximab, which destroys cancerous B-cells by attaching to the CD20 antigens expressed on those cells, and CHOP, a form of chemotherapy because of their separate mechanisms of action." Pet. at 43. At a minimum, this rationale fails because Petitioner has not proven that rituximab and CHOP have separate mechanisms of action in treating DLCL. Instead, Petitioner focuses on mechanisms of killing B cells—and only on such a mechanism for rituximab. Petitioner asserts

that rituximab "destroys cancerous B-cells by attaching to the CD20 antigens expressed on those cells," but does not assert a mechanism of action for CHOP (or any of its components). It has therefore failed to set forth any proof of separate mechanisms of action, regardless of what it means by that term.

Petitioner cites *Novo Nordisk A/S v. Caraco Pharmaceutical Laboratories, Ltd.*, 719 F.3d 1346, 1351 (Fed. Cir. 2013), for the proposition that it is "obvious to try combination therapy," where "[i]t was apparently well-known in the art that two drugs having different mechanisms for attacking [the disease] may be more effective than one." Importantly, Petitioner did not provide any evidence showing that it was known in the art that rituximab and CHOP have different mechanisms for attacking DLCL as the term is used in *Novo Nordisk*. Petitioner confuses the biological "mechanism" of action at the molecular level with the "mechanism of attacking a disease" addressed in *Novo Nordisk*. *See* Pet. at 43 (describing rituximab's attachment to CD20 antigens).

In *Novo Nordisk*, the focus was on diabetes, a field in which it was already "well-known in the art that two drugs having different mechanisms for attacking diabetes may be more effective than one." 719 F.3d at 1351. Specifically, "[c]ombination therapy using insulin sensitizers and insulin secretagogues was common at the time." *Id*. Thus, to the extent that there was any suggestion in *Novo Noridsk* that there is a motivation to combine two different drugs simply because they have different mechanisms for attacking a

disease (there is not), that rationale is inapplicable here because Petitioner did not prove (or even try to prove) that CHOP and rituximab have different mechanisms for attacking DLCL.

D. A skilled artisan would not have had a reasonable expectation of success in combining Shipp and Link to arrive at the claimed methods.

Institution also must be denied because Petitioner has failed to establish that a POSA would have had a reasonable expectation of success in combining Shipp and Link to yield the claimed invention. Petitioner does not attempt to carry this burden. This is not entirely unsurprising, given that Petitioner failed to articulate a specific proposed change to Shipp in light of Link's teachings, instead offering suggested routes of experimentation grounded solely in hindsight. And as explained in detail below, the prior art in fact would have negated any reasonable expectation of success in treating the claimed patients at the time of the invention.

1. Petitioner does not even try to set forth a reasonable expectation of success.

Under the heading "Motivation to combine", Pet. § IX.A.1.d, Petitioner sets out a number of purported rationales for combining Shipp and Link. Those rationales are rebutted above in § IV.D. But even if Petitioner had established a reason to combine references (it has not), that standing alone would not be enough to prove obviousness. *See Broadcom Corp. v. Emulex Corp.*, 732 F.3d

1325, 1335 (Fed. Cir. 2013). Petitioner must also prove that a POSA would have had a reasonable expectation of success in making the invention. *Amgen Inc. v. F. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1362-63 (Fed. Cir. 2009). In no way does Petitioner attempt to explain why or how a POSA would have had a reasonable expectation of success in combining Shipp and Link to arrive at the claimed invention.

The only mention of the required reasonable expectation of success is a conclusory citation to *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012), quoting the case as support for Petitioner's bare conclusion that "a skilled artisan would have had a reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." Pet. at 43-44. Parroting the legal standard is not a substitute for providing supporting evidence.

Petitioner further cites Dr. Ozer's declaration, Ex. 1002, ¶¶ 80-81, but Dr. Ozer does not cure Petitioner's failure of proof. The cited passages from his declaration are silent regarding reasonable expectation of success. They merely rehash the claim elements purportedly taught by the references and offer a conclusory statement that combining those elements "was obvious." "Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight." *See* 37 C.F.R. §42.65(a);

ActiveVideo Networks, Inc. v. Verizon Commc'ns., Inc., 694 F.3d 1312, 1327 (Fed. Cir. 2012) (discounting expert testimony where the expert "never provided any factual basis for his assertions"); *Delphix Corp. v. Actifio, Inc.*, No. IPR2015-01678, 2016 Pat. App. LEXIS 1027, at *27 (P.T.A.B. Feb. 10, 2016) (denying institution where Petitioner relied on "conclusory expert testimony that, itself, does not cite to evidentiary support").

Here, Petitioner's failure to even attempt to establish a reasonable expectation of success in combining the cited references to achieve the claimed invention is fatal to Petitioner's ability to meet its burden to demonstrate a reasonable likelihood that at least one claim is unpatentable for obviousness. *See, e.g., Broadcom*, 732 F.3d at 1335 (affirming district court's finding of nonobviousness) ("Even assuming that a person of ordinary skill might have some motivation to add a data path to Pickering, the record does not show any reasonable expectation that this significant change would be successful."); *see also BioGatekeeper, Inc. v. Kyoto Univ.*, No. IPR2014-01286, 2015 WL 604984, at * 5-6 (P.T.A.B. Feb. 11, 2015) (denying institution because Petitioner failed to establish that a POSA would have had a reasonable expectation of success in achieving the claimed combination).

Petitioner does not state how or why a POSA would expect success in treating elderly DLCL patients with bulky disease—known to be particularly susceptible to CHOP's toxicity—by somehow incorporating Link's R-CHOP

regimen into Shipp's high-dose CHOP regimen, which carried with it a demonstrated risk of life-threatening toxicity. Not only has Petitioner failed to explain how a POSA supposedly would have combined the two different regimens, it has failed to set forth why a POSA supposedly would have expected success. Nor could it. As set forth below in §§ IV.D.2-IV.D.4, the art suggested that a POSA would expect failure.

2. A POSA would not have expected success in combining rituximab with CHOP therapy due to significant toxicity concerns associated with each therapy individually.

As explained in detail above in § IV.C.2, even in standard CHOP therapy using normal cyclophosphamide and doxorubicin doses (as compared to Shipp's high-dose regimen), POSAs were especially concerned that CHOP therapy was ***unduly toxic*** when used to treat elderly patients with aggressive NHL. *See* § II.C.4. Petitioner does not explain how a POSA supposedly would have expected success in combining Shipp's CHOP regimen—already believed to give rise to synergistic cardiotoxicity concerns—with rituximab—independently known to cause cardiac hypotension and arrhythmia. Petitioner's failure to address these significant independent downsides of each therapy in its proposed combination is fatal to establishing that a POSA would have had a reasonable expectation of success.

3. A POSA would not have had a basis to expect that adding rituximab to the highly-toxic Shipp protocol would create a regimen with acceptable toxicity.

Petitioner appears to frame success in combining Shipp and Link as "improved efficacy without increasing toxicity." Pet at 41; *see also id.* at 42 (noting desire for drug combinations "as effective but less toxic than [standard] CHOP") (quoting McNeil). But Shipp's extreme toxicity, resulting in serious adverse events in all patients, *see* §§II.C.1 and II.C.5, negates any expectation of success—even in the manner framed by Petitioner. Indeed, as discussed in § II.C.1 above, Shipp teaches that the toxic doses of chemotherapy are necessary to its alleged efficacy. That is why Shipp tried its high-dose regimen despite the fact that life-threatening Grade 4 adverse events were "expected." Ex. 1009, 3.

As the Federal Circuit held in *Institut Pasteur v. Focarino*, where a reference "specifically teaches" that its methods "could be 'highly toxic,'" such a teaching "counts significantly against finding a motivation to take the claimed steps with a reasonable expectation of success." 738 F.3d 1337, 1345 (Fed. Cir. 2013). In *Institut Pasteur*, the claims were directed to a method of modifying chromosomal DNA in cells using certain gene targeting methods. *See id.* Here the claims are directed to methods of treating human patients—even more reason for a skilled artisan not to take lightly steps which could be "highly toxic" to the patient. The Board and Petitioner cannot "disregard [Shipp's] toxicity teaching," admitted by Dr. Ozer, in assessing the absence of

a reasonable expectation of success in combining the cited references to achieve the claimed invention. *Id*. at 1346.

4. Petitioner has not explained how a POSA could have successfully combined Shipp and Link to maintain Shipp's purported efficacy while reducing its toxicity.

(a) The dosing regimens of Shipp and Link differ significantly.

Petitioner failed 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). Here, the amount of chemotherapy drugs used and the specific administration protocols of Shipp and Link differ so significantly that a POSA would not know how to combine them. Petitioner's arguments are simply invitations to experiment, where the only indication of possible success comes from the hindsight that the claimed invention was in fact successful.

To support a conclusion of obviousness, Petitioner must do more than baldly state that a POSA, "once presented with the two references, would have understood that they *could be* combined." *Id.* at 993-94 (emphasis original). Here, all four dose levels of the treatment regimen used in Shipp are used for only four cycles, each using roughly four to five times the cyclophosphamide dose, and up to nearly two times the doxorubicin dose conventionally used in

the art. *See* § II.C.5; Ex. 1009, 2. Link, on the other hand, exclusively utilizes a conventional six-cycle, lower-dose CHOP scheme. Ex. 1005, 5.

At all four dose levels, Shipp's patients further received supporting doses of G-CSF and mesna to attempt to counteract the negative effects of the high dose CHOP. Ex. 1009, 2, 4. The Shipp protocol required a carefully planned schedule for administering these drugs to try to control toxicity, including dividing doses of cyclophosphamide and doxorubicin, and administering the former in bolus doses and the latter as a continuous infusion over 48 hours, all to try to limit cardiotoxicity. *Id*., 2. Nevertheless, all patients suffered serious side effects, including grade 4 life-threatening or disabling events. *See* §§II.C.1; II.C.5.

Link, on the other hand, explicitly teaches six cycles of R-CHOP, where the cyclophosphamide is administered at a dose of 750 mg and vincristine at 50 mg. Ex. 1005, 5. Link's regimen involves the administration of the rituximab dose on Day 1, followed 48 hours later by CHOP. *Id*. Unlike Shipp, Link does not split the administration of any of the CHOP components, or require multi-day infusions, in order to manage cardiotoxicity or any other side effect.

Put simply, the two regimens are incompatible in numerous ways, including number of cycles (four as opposed to six); order of administration; form of administration (*e.g.*, multi-day infusion); division of doses; and use of an accompanying G-CSF regimen for its administration. On top of these

differences in administration methods, the regimens fundamentally differ in their significantly different overall doses of each component of CHOP.

Petitioner provides no evidence from the prior art that would guide a POSA to harmonize these many variables, much less what effect the various permutations would have on safety and efficacy. Nor does it provide a reasoned explanation or set of scientific principles that purportedly would have guided a POSA in making these myriad choices with a reasonable expectation of success. Petitioner thus failed to show how its proposed combination of Shipp and Link "was supposed to work." *Pers. Web Techs. LLC*, 848 F.3d at 994.

(b) Petitioner has not provided any evidence showing that a POSA would have expected success in utilizing rituximab to somehow modulate the toxicity of Shipp's high-dose CHOP regimen.

Petitioner's proposed combination of references has numerous variables, and Petitioner has not explained why a POSA supposedly would have believed that adding rituximab would "reduce the toxicity" of Shipp, given the significant differences in the therapies proposed by the two references. The required detail and explanation of how to combine these differing regimens is simply absent from Petitioner's papers.

Petitioner does not explain how the numerous drugs in its proposed combination can safely be co-administered. For example, Shipp teaches that

the administration of G-CSF was necessary in an effort to control the toxicity-related side effects of the high CHOP dosages used. Ex. 1009, 3-4 ("Presumably, patients on dose levels one to three did not have significant dose-related differences in their neutropenia ***because they were supported with G-CSF during each cycle of therapy***.").[11] However, Meyer concluded, specifically in the context of treating elderly patients with aggressive NHLs, that "[e]scalating the dose of cyclophosphamide within CHOP to 900 mg/m^2 [*cf.* Shipp's 3000-4000 mg/m2] for 6 treatment cycles ***does not appear to be feasible even with G-CSF***." Ex. 2009, 2-3. Meyer proposed using G-CSF specifically to "reduce the toxicity associated" with chemotherapy in order to try to administer higher dose intensity and more doses. Ex. 2009, 3.

In other words, Meyer tried to use G-CSF to mitigate the toxicity of cyclophosphamide in elderly patients, and failed, even when the cyclophosphamide dose was only 120% of standard (as opposed to Shipp' 400-533%). Meyer also found that reducing drug doses or scheduling them less frequently to assuage toxicity concerns in elderly patients "produce[d] results inferior to those achieved with the standard combination of [CHOP]." Ex. 2009, 3.

[11] Petitioner does not state whether the proposed combination would even include G-CSF.

A POSA would not have expected Petitioner's proposed combinations to be successful, regardless of how the proposed modifications were actually made. The art shows that starting with Shipp and simply adding rituximab, even with G-CSF support, would result in unacceptable levels of toxicity. And reducing either the amount or frequency of CHOP resulted in "inferior" efficacy compared to standard CHOP.

As another example, Petitioner never explains how a POSA would know how to successfully modify Shipp's regimen to avoid "synergistic cardiotoxicity" when trying to convert from four to six cycles, and adjusting doses. *See* § IV.C.4. "[A]n invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution." *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009). When the prior art amounts to an invitation to experiment in a field, but gives minimal "guidance as to the particular form of the claimed invention or how to achieve it," the claimed invention is not "obvious to try." *Id*. Thus, following Petitioner's reasoning, a POSA would not have expected success in combining Shipp and Link to arrive at the claimed method.

V. GROUND II: SHIPP IN VIEW OF COIFFIER

Ground II relies on Shipp and Coiffier as purportedly disclosing various individual claim limitations. Ground II fails because Petitioner fails to establish that a POSA would have had a reason to modify Shipp's regimen with a

reasonable expectation of success in the claimed patients by adding Coiffier's rituximab monotherapy. Coiffier reported that rituximab failed in treating patients with bulky tumors ≥10 cm in diameter and expressed skepticism in using intensive combination therapy, directing the POSA away from the proposed combination. And Ground II is also plagued by the same toxicity and interoperability concerns as Ground I. Institution should be denied.

A. Shipp and Coiffier fail to disclose the treatment of an elderly DLCL patient presenting with bulky disease.

Petitioner does not allege that any additional disclosures in Shipp are relevant to this ground. As discussed above in §§ II.C.1 and IV.B, Shipp fails to disclose the treatment of even a single elderly patient with DLCL presenting with bulky disease, and further fails to provide any disclosures relevant outside of the context of ***high-dose*** CHOP therapy. Coiffier fails to remedy Shipp's deficiencies, and further emphasizes that a POSA would have been concerned with the toxicity of intensive chemotherapy in elderly patients. *See* § II.C.3.

B. Petitioner fails to establish any reason to combine Shipp and Coiffier.

1. Coiffier counsels against combining rituximab with intensive chemotherapy in elderly patients.

Petitioner suggests that Coiffier's passive assertion that "Rituximab has significant activity in DLCL and MCL patients and should be tested in combination with chemotherapy in such patients," provided a POSA with the

required motivation to "add the anti-CD20 antibody rituximab to the CHOP chemotherapy of Shipp." Pet. 45-46. A POSA would not have been so motivated, particularly with respect to the claimed elderly patients with bulky disease.

Coiffier suggests combining rituximab with "***standard chemotherapy*** in patients with aggressive B-cell lymphoma." Ex. 1006, 6. It is important to note however, that Coiffier distinguishes between single agent chemotherapy, combination chemotherapy, and high-dose chemotherapy. Indeed, Coiffier explicitly recognized that high-dose chemotherapy had "been associated with a much higher toxicity, particularly hematologic toxicity," in elderly patients, and as such was contraindicated and not used in that population. *Id.*, 5.

As set forth above and as noted repeatedly by Petitioner, Shipp's chemotherapy regimen was "high dose," even in the context of combination chemotherapies. Coiffier explicitly distinguishes between combination chemotherapy, which it notes carries with it "characteristic toxicity," and "standard chemotherapy." For example, Coiffier compares the response rates of its rituximab monotherapy protocol with "what would be expected with single-agent therapy in this patient population." *Id*. at 5.

Coiffier then compares such "single-agent," or standard therapy, to "combination chemotherapy" regimens, which "are often used in younger patients and have been associated with a much higher toxicity, particularly

hematologic toxicity." *Id*. Coiffier notes that a direct comparison with combination chemotherapy is not possible because "elderly patients are commonly excluded or underrepresented in published trials" due to toxicity. *Id.* at 6.

Coiffier further suggests that its rituximab protocol, which involves "a single agent administered for 8 weeks," is incompatible with "intensive, high-dose chemotherapy regimens administered over several months." *Id*. at 6. Thus, read in context, Coiffier discourages combining rituximab with "intensive, high-dose chemotherapy regimens" like Shipp. *Id.* While it appears Coiffier would consider even standard CHOP an inappropriate "intensive high-dose" chemotherapy regimen, there is no debate that Shipp's regimen is substantially more intense, contains extremely high chemotherapy doses, and would not be considered "standard" under Coiffier's (or any other) definition.

Moreover, Coiffier was not limited to elderly patients. Coiffier reports that only "50% and 62% of patients enrolled were older than 60 years in arms A and B, respectively." *Id*. at 6. Given the overall response rate of only 33%, *Id.* at 3, it is thus not apparent that any of Coiffier's statements regarding evaluating rituximab in combination with chemotherapy (whether standard or combination) are referring to the elderly patient population. One cannot tell from Coiffier to what extent (if any) elderly patients responded to therapy. Indeed, consistent with McNeil, Coiffier notes that "elderly patients are

commonly excluded or underrepresented" in trials of chemotherapy, and further notes that "combination chemotherapy regimens" carry with them a risk of "characteristic toxicity" (in patients of all ages). *Id*., 6. Thus, Coiffier does not support Petitioner's proposed combination of rituximab with "characteristic[ally] toxic" combination chemotherapy in elderly patients. At most Coiffier makes a bare proposal to try a rituximab in combination with standard chemotherapy, which as the term is used in the paper, appears to refer to single agent chemotherapy. *See* Ex. 1006, 5-6. Such a proposal does not render the claims obvious. *See Procter & Gamble Co.*, 566 F.3d at 996–97 (courts should not succumb to hindsight claims of obviousness where only guidance in the art is at most an invitation to experiment).

2. Petitioner's rebuttals to "teaching away" arguments made during prosecution do not provide an affirmative reason to combine.

Petitioner attempts to set forth two additional reasons to combine Shipp with Coiffier, framed as rebuttals to arguments made by Applicant during prosecution. Petitioner states that "a POSA would have been motivated to combine rituximab with CHOP precisely because Coiffier taught that rituximab *monotherapy*—i.e., without other drugs—was insufficient to treat tumors ≥10 cm in diameter." Pet. at 47. Petitioner cites Coiffier's 21% response rate in treating lesions between 5 and 10 cm, and 46% response rate in tumors less than 5 cm as suggesting that "a POSA would have been motivated to

investigate combination therapy with rituximab—especially combination with another drug (or drugs) that would reduce the size of such large tumors such that they could be effectively treated with rituximab, as taught by Coiffier." *Id*. at 48.

Petitioner further relies on Dr. Ozer's statement that "Coiffier's data then would have taught that rituximab could treat the tumors once reduced in size." *Id*.; Ex. 1002, ¶ 88. But Petitioner neither provides evidence that POSAs pursued such a course of sequential therapy to target bulky disease, nor provides any evidence that rituximab works on tumors that have been partially reduced in size by prior chemotherapy treatment. In fact, the art, including Coiffier, distinguishes between patients that have previously been treated with chemotherapy and patients who were not previously treated. *See* Ex. 1006, 3 ("Only 9 patients (17%) were previously untreated, 17 (31%) were in first relapse, and 23 patients (43%) were in progressive disease after failure or partial response to their first chemotherapy treatment."). This suggests that POSAs did not expect additive responses to therapies administered in sequence.

Petitioner's assertion that Coiffier's success using rituximab in "smaller" tumors suggests that all a POSA would need to do is make the patient's bulky tumors small first is an oversimplification that lacks supporting evidence. Tellingly, Coiffier makes no observation that any unmentioned "smaller

tumors" present in its patients responded to rituximab monotherapy. To the contrary, Coiffier states "no responses were observed in patients whose largest tumor was greater than 10 cm in diameter." Ex. 1006, 4. The use of the word "largest" suggests that these bulky disease patients may have had smaller tumors as well, but such tumors are not discussed and there is no data indicating that such tumors responded to therapy in bulky disease patients (or any other patients).

In short, no response means ***no response***. A POSA reviewing Coiffier's results regarding the bulky disease patients treated in its study would not read the 0% response rate reported in Table 3 and interpret that to mean the patient's (unmentioned) "smaller tumors" improved as a result of treatment.

Thus, Coiffier provides no evidence for Petitioner's assertion that the patients' smaller tumors responded, and in fact further shows that Petitioner's "make the tumors small first" theory oversimplifies the nature of bulky disease by assuming that the sole issue is tumor size, as opposed to the characteristics of the particular patients' disease that cause it to become bulky. As recognized by Shipp, patients with bulky disease have a poor prognosis and respond to therapy differently from other patients. Ex. 1009, 1. Petitioner has failed to establish that the sole issue rendering bulky disease difficult to treat is the size of the tumor, and not the underlying biologic characteristics of the tumor that cause it to grow into a bulky tumor in the first place. Thus, simply making

bulky tumors less than 10 cm in diameter before adding another therapy (assuming such a thing is even possible)[12] would not suggest that rituximab would be effective in treating the "reduced" bulky tumors, particularly in light of Coiffier's reported lack of success in treating bulky tumors ≥10 cm in diameter with rituximab. The lack of any reported response in these patients negates any purported reason to combine.

C. A POSA would not have had a reasonable expectation of success in combining Shipp and Coiffier to arrive at the claimed methods.

As with Ground I, and as explained above in § IV.D, Petitioner provides no evidence that a POSA would have a reasonable expectation of success in combining Shipp and Coiffier to arrive at the claimed invention. Just the opposite, in fact, as Coiffier found that rituximab was unsuccessful in treating patients with tumors ≥10 cm in diameter. In addition, the combination of Shipp and Coiffier is plagued by the same toxicity-related safety concerns and unexplained interoperability as the combination of Shipp and Link. And again, not only does Petitioner fail to address reasonable expectation of success, its cited art actually negates any such expectation.

[12] Petitioner does not set forth any evidence justifying such an approach, other than speculation.

1. CHOP and rituximab monotherapy had each been individually unsuccessful in the claimed patient population.

Coiffier emphasizes that high-dose chemotherapy had "been associated with a much higher toxicity, particularly hematologic toxicity," in elderly patients, and as such was contraindicated and not used in elderly patients. Ex. 1006, 5. Coiffier further shows a lack of success in treating patients with lesions ≥10 cm in diameter. *Id.* at 3, Table 3. As set forth in detail above in § IV.D.2, a POSA would have had significant concerns that combining the two therapies would harm patients. Thus, they would not reasonably expect success.

2. The severe toxicity of the Shipp regimen negates any reasonable expectation of success.

As set forth in § IV.D.3, a POSA would not have expected success as a result of Shipp's significant toxicity concerns. The Shipp regimen's extreme toxicity, in combination with elderly patients' well-known intolerance for CHOP's toxicity (even at standard doses), suggests that a POSA would instead have been highly skeptical of successfully using Shipp's regimen as a starting point in elderly patients. This skepticism is confirmed by Coiffier. *See* § V.B.1. Indeed, Shipp's reports of high frequencies of serious adverse events, confirmed by Petitioner's expert, show that a POSA would have been fearful of giving Shipp's high doses to elderly patients. *See* § IV.D.3.

3. Petitioner has not explained how a POSA could have successfully combined the two references to maintain the purported efficacy of Shipp while reducing its toxicity.

For all the reasons set forth in § IV.D.4, Petitioner failed to "clearly explain[], or cite evidence showing, *how* the combination of [] references was supposed to work." *Pers. Web Techs. LLC.*, 848 F.3d at 994. Further, Petitioner has not explained how to implement Coiffier's use of rituximab with the Shipp regimen, given that Shipp requires the use of a 21-day cycle, whereas Coiffier administered rituximab weekly for 8 weeks. Ex. 1006, 1, 2. Coiffier notes that a comparison of its study of rituximab as a "single agent administered for 8 weeks," with "intensive, high-dose chemotherapy regimens administered over several months" (*e.g.* the Shipp regimen), "is not appropriate." *Id.* at 6. This further counsels away from simply combining the regimens by adding rituximab to Shipp's CHOP (or vice versa), and suggests that, at best, significant experimentation would be required in order to successfully arrive at the claimed combination therapy.

VI. CONSTITUTIONALITY 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*, 198 L. Ed. 2d 677 (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.").

VII. CONCLUSION

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

Dated: August 8, 2017

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, the undersigned certifies that on August 8, 2017, a copy of the foregoing document **BIOGEN, INC.'S PATENT OWNER PRELIMINARY RESPONSE, Patent Owner's Exhibit List** and **Exhibits 2001, 2004-2005, 2008-2013, and 2015-2017** 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 13,941 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: August 8, 2017

Respectfully submitted,

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