UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,

Petitioner,

v.

BIOGEN, INC.,
Patent Owner.

Case IPR2018-00231
U.S. Patent No. 9,504,744

PATENT OWNER PRELIMINARY RESPONSE

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I. INTRODUCTION

The patent challenged here, U.S. Patent No. 9,504,744 ("the '744 patent"), contains two groups of claims. One group—Claims 11-12 and 15-16—requires treating patients >60 years old ("elderly patients") suffering from diffuse large cell lymphoma (DLCL) by administering rituximab and CHOP chemotherapy[1] wherein the rituximab and CHOP are given "concurrently" or both on "Day 1 of each chemotherapy cycle." These claims are challenged in Grounds I and III of the Petition as obvious over proposed combinations of four or five references. The other group of claims—Claims 1-10 and 13-14—requires treating DLCL elderly patients using CHOP and rituximab "in combination with a transplantation regimen." These claims are challenged in Grounds II and IV as obvious. Each of Petitioner's grounds fails.

Grounds I and III: Claims 11-12 and 15-16

For the first group of claims, the Petition fails to cite *any* reference that taught administering CHOP and rituximab concurrently or both on Day 1. To the

[1] "CHOP is an acronym…describ[ing] a chemotherapy regimen that consists of cyclophosphamide, hydroxydaunorubicin (also referred to as doxorubicin or Adriamycin®), Oncovin® (or vincristine), and prednisone (or prednisolone)." Pet. 1, fn 1.

contrary, the prior art *only* taught administering rituximab and CHOP on different days.

Petitioner's only cited reference disclosing a dosing regimen for rituximab and CHOP (Link, Ex. 1005) taught administering them on different days. Another clinical study that Petitioner relies on in IPR petitions against other patents in the rituximab portfolio—but not in the petition at issue here—also taught administering rituximab and CHOP on different days (Czuczman, Ex. 2001). And that clinical reference, which was published before the priority date, expressly explained that rituximab and CHOP were given on different days for efficacy reasons.

It was known, for example, that administering rituximab as *pretreatment* before administering CHOP sensitized cancer cells to the doxorubicin (H) in CHOP, promoting the destruction of cancer cells. It was also known that CHOP chemotherapy weakens aspects of the immune system on which rituximab relies to destroy B cells, and thus would inhibit the effectiveness of rituximab if given on the same day.

Moreover, administering rituximab and CHOP on the same day would have raised significant toxicity concerns. It was known, for example, that CHOP even by itself was highly toxic to elderly patients (the claimed patient population). And historically, when clinicians added drugs to the components of CHOP, they did so

by administering different drugs on different days. Likewise, clinicians separated the administration of rituximab, a relatively novel drug at the time, and CHOP "to limit the possibility of additive toxicities" by providing for a wash-out period that allowed clinicians to monitor for toxicity following administration of each therapy. There was no safety data in the literature for administering rituximab concurrently with any chemotherapy regimen, let alone CHOP.

Petitioner argues that "general knowledge" and "convenience" would have motivated a POSA to administer rituximab and CHOP concurrently or both on Day 1. But this "general knowledge" argument is not supported by any reference, and Petitioner's expert only repeats the conclusory assertions of the Petition. For its "convenience" argument, Petitioner cites an article that fails to support Petitioner's argument that expenses "would have increased significantly with an additional outpatient visit." Pet. 45. Even assuming that the article applies to administration of rituximab and CHOP days apart (it does not), the article found that nonmedical costs increased modestly by only twenty-seven dollars during weeks when the patient received therapy.

In any event, Petitioner fails to establish that any alleged convenience or cost considerations would have outweighed the proven practice of administering rituximab and CHOP on separate days, for efficacy and toxicity reasons, as the best means of curing the lethal disease DLCL. Petitioner's expert has conceded that

"efficacy and toxicity were *the* critical parameters for designing a treatment regimen for DLCL patients over 60 years old." Ex. 2002 at 59:16-19.[2] Thus, a POSA would not have been motivated to combine the cited references to arrive at the claimed invention.

Nor would a POSA have had a reasonable expectation of success for administering rituximab and CHOP concurrently or both on Day 1 in elderly patients with DLCL. It was known that such patients experience severe toxicity, often requiring hospitalization, even with CHOP chemotherapy by itself. Petitioner's expert has conceded that the toxicity for elderly patients is so severe that they were thought to be "unable" to receive a full regimen of six to eight cycles of CHOP.

None of Petitioner's cited references disclosed any clinical results for administering rituximab and CHOP to patients over 60, as claimed. While Petitioner's primary reference, Link (Ex. 1005), did administer rituximab and CHOP (*on different days*) to intermediate- or high-grade NHL patients, some of

[2] Emphasis is added in this Preliminary Response unless otherwise noted. Petitioner's expert, Dr. Howard Ozer, was deposed in an IPR proceeding for the parent patent, U.S. No. 8,821,873, with the same priority date of August 11, 1999. Petitioner has also adopted that date as the priority date for purposes of this IPR. Pet. 10.

whom were DLCL patients, Petitioner concedes that "Link did not study patients over 60." Pet. 20. None of Petitioner's other cited references fill in the gaps left by Link.

Grounds II and IV: Claims 1-10 and 13-14

Petitioner's obviousness arguments against the second set of '744 patent claims, *i.e.*, those describing administering CHOP and rituximab "in combination with a transplantation regimen," fare no better. Critically, the Petition fails to cite any art that discloses administering rituximab *in combination with*, i.e., during, a stem cell transplantation regimen.

Petitioner argues that Maloney (Ex. 1009) "suggested combining rituximab…with stem-cell transplantation." Pet. 22. The cited portion of Maloney, however, suggests using rituximab "*following*" a transplantation regimen, not *during* any stage of the transplantation regimen. Ex. 1009 at 10.

Petitioner also relies on a textbook chapter discussing stem cell transplantation (Armitage, Ex. 1008) to argue that a POSA would have been "motivated…to add a transplantation regimen if initial induction therapy with rituximab and CHOP failed." Pet. 36. But the phrase "induction therapy" appears nowhere in Armitage. Nor do "CHOP" and "rituximab." Petitioner fails to cite any art indicating that rituximab or CHOP was given as induction therapy during a transplantation regimen.

Nor would there have been a reasonable expectation of success using rituximab, CHOP, and a transplantation regimen to treat elderly patients. A POSA would have known that the toxicity risk would have increased substantially by adding a "potentially lethal" transplantation regimen. A transplantation regimen by itself is so toxic that most elderly patients could not use it "because of . . . an unacceptably high treatment-related death rate." *See* Ex. 2003 at 6. Because of these toxicity concerns, Petitioner has failed to establish a reasonable expectation of success for using rituximab, CHOP, ***and*** a transplantation regimen to treat elderly patients.

Dependent Claims 7, 9, 13-14 further require that rituximab and CHOP are administered concurrently or both on Day 1, and are not obvious for reasons discussed above for Grounds I and III.

For all these reasons, and the further reasons articulated below, Petitioner has not established a reasonable likelihood of prevailing on any articulated Ground.

II. BACKGROUND

A. Diffuse Large Cell Lymphoma

Non-Hodgkin's lymphomas (NHLs) are cancers that target the body's lymphatic system, and are characterized by the uncontrolled growth of the body's B-cells. Ex. 1014 at 35. "[N]on-Hodgkin's lymphomas constitute a heterogenous

[sic] group of neoplasms of the lymphoid system that include distinct entities defined by clinical histologic, immunologic, molecular, and genetic characteristics." Ex. 1010 at 1.

One determining factor for a patient's prognosis was (and remains) the grade of lymphoma: low, intermediate, or high. *Id.* Low-grade (LG) lymphomas, unlike intermediate- and high-grade (IG/HG) lymphomas, grow more slowly. Ex. 1011 at 2-3; Ex. 1010 at 3-5. Intermediate- and high-grade NHL patients have an aggressive form of NHL marked by rapidly growing tumorous cells; but they were curable with proper treatment. *Id.*

Within the general category of intermediate-grade lymphomas, there were different histological forms of lymphoma that determined the patient's prognosis and treatment choice, such as mantle cell lymphoma, diffuse small cleaved lymphoma, diffuse mixed lymphoma, and diffuse large cell lymphoma (DLCL). Ex. 1011 at 2. The claimed invention is limited to this last lymphoma histology—DLCL—which was identified as "Type G" by the International Working Formulation ("IWF"), and classified as "aggressive" under the Revised European American Lymphoma ("REAL") classification. Ex. 1011 at 2.

B. Treatments of DLCL

1. First-Line Chemotherapy

Upon diagnosing a patient with DLCL, physicians would strive to drive the disease into remission. The first treatment administered to the patient was called "first-line" or "front line" treatment. This could be one therapy or a course of therapies. A single "line" or "course" of treatment referred to one or more therapies administered together or in succession without the patient relapsing in between.

Patients with DLCL were typically treated with chemotherapy, such as CHOP, as first line treatment to induce the cancer into remission. *See* Pet. 2 ("standard of care in the art as of August 1999 was to use 'full-dose' CHOP chemotherapy in six to eight cycles as a first-line treatment for patients"); Ex. 1002 ¶ 38-39; Ex. 1014 at 42-43. Each cycle of a CHOP regimen was administered over five days typically in 21-day cycles. *See* Pet. 19; Ex. 1005 at 7.

The standard CHOP regimen used for inducing remission in DLCL patients was 6 to 8 cycles of CHOP. Pet. 2. These CHOP regimens produced complete responses in 50-60% or more of DLCL patients. Ex. 2002 at 28:18-22. But not all of those patients experienced long-term remission or cure. Many patients would relapse.

2. Salvage Treatment With Stem Cell Transplantation Regimens

When a patient relapsed, the patient would receive further treatment called "salvage therapy." *See* Ex. 1013 at 12. The CHOP regimen, however, could not be used as salvage therapy for relapses after first-line CHOP treatment because there is a lifetime limit on the amount of doxorubicin a patient can receive, and that limit "was reached with 8 standard doses [or cycles] of CHOP. *See* Ex. 2002 at 37:3-6; Ex. 2004 at 3 (explaining that the "risk of developing CHF [congestive heart failure] increases rapidly with increasing total cumulative doses in excess of 450 mg/m^2 of doxorubicin").[3]

Instead, one strategy for treating relapsed IG/HG lymphoma patients was to use a stem cell transplantation regimen. This involved administering very high amounts of a chemotherapy regimen such as BACT, TACC, BEAM, BAVM, CBV, ABV, melphalan, and BAC. *See* Ex. 2005 at 3; Ex. 1002 ¶ 39-40. Because such high amounts of chemotherapy wiped out the patient's bone marrow, physicians would then infuse stem cells to help restore the patient's immune system. Ex. 1008 at 4. These stem cells could be harvested directly from bone marrow, as part of a "bone marrow transplantation" (BMT) regimen, or from

[3] Each doxorubicin dose in CHOP is typically given at 50 mg/m^2 (so 400 mg/m^2 total for eight cycles). *See* Pet. 4.

circulating blood, as part of a "peripheral [blood] stem cell transplantation" (PBSCT) regimen. Ex. 1008 at 5. "Allogeneic" transplantation regimens used stem cells from another person "whose bone marrow matche[d]" the patient's, while "autologous stem cell transplantation" (ASCT) regimens used a patient's own stem cells. Ex. 1008 at 4.

A transplantation regimen could involve several stages: induction, in vivo purging, mobilization, harvesting, conditioning, and reinfusion. *See* Ex. 1001 at 5:66-6:58. "Induction" with initial therapies during a transplantation regimen was aimed at achieving induction of remission prior to harvest. *Id*. at 6:33-36. When stem cells were harvested from the bone marrow, the transplant regimen could include an "in vivo purging" stage to reduce the number of cancer cells in the marrow to be extracted. *See id.* at 6:37-43. When stem cells were harvested from the peripheral blood, a "mobilization" step could be used to push stem cells out of bone marrow and into circulation. *Id.* at 6:48-59. "Harvesting" is the removal of stems cells from either the bone marrow or peripheral blood. *Id.* at 6:41-43. After harvest, "conditioning" is done, typically with the "very high dose chemotherapy" discussed above, "to deplete all bone marrow cells, i.e., both healthy cells and tumor cells, from the bone marrow." *Id.* at 6:62-67. Finally, stem cells are reinfused back into the patient's blood. *Id.* at 6:58-59.

The toxicity risk of transplantation regimens was high. It was known to be a "potentially lethal" therapy. *See* Ex. 2002 at 38:11-14. Toxicity was particularly acute for elderly patients, to the point that elderly patients were not even eligible for ABMT regimens because of "an unacceptably high treatment-related death rate." Ex. 2003 at 1028.

Because of the risks involved with a transplantation regimen, it was typically reserved for patients who had responded to first-line chemotherapy, subsequently relapsed, but still had chemosensitive disease. *See* Ex. 1013 at 12. "In [non-chemosensitive] patients who have never been in CR [complete response] ('primary refractory') and patients whose disease is resistant to salvage chemotherapy at the time of relapse ('resistant relapse')," transplantation resulted in poor outcomes and was not recommended. *Id.*

C. Treatment of DLCL Patients >60 Years Old

As of the priority date, a POSA would have known that age was a critical prognostic factor for DLCL. "[A]ge—being over age 60—was the most important factor independently associated with poorer survival in patients with intermediate- and high-grade lymphoma." Ex. 1006 at 1. Elderly patients were known to have "inferior outcomes" with therapy because of "differences in disease biology," "more frequent relapses from a remission state," "increased susceptibility to the

toxic effects of chemotherapy and more treatment-related deaths," and "an increased prevalence of comorbid conditions." Ex. 1004 at 4, 10.

"DLCL patients over 60 were at higher risk of suffering adverse effects from the standard CHOP treatments and were less likely to respond to the standard treatment methods." IPR2017-01168, Ex. 1002, ¶ 52 (statement by Petitioner's expert). CHOP was known to cause more adverse events in patients >60 years old, Ex. 1006 at 1 (stating that CHOP "is more toxic in [the elderly] age group"), because they had "increased susceptibility to the toxic effects of chemotherapy and more treatment-related deaths." Ex. 1004 at 4. And CHOP reportedly cured "only about half as many elderly patients as younger patients." Ex. 1006, 1.

Elderly patients also experienced greater toxicity and had poorer outcomes with transplantation regimens. "[A]utologous bone marrow transplantation . . . [could not] be used for most elderly patients because of poor tolerance and an unacceptably high treatment-related death rate." Ex. 2003 at 1028. And elderly patients were not even eligible for allogenic transplantation. Ex. 1008 at 6 (identifying the "oldest age to which [allogeneic transplant is] applicable" as "40-55").

D. Rituximab

Rituximab is an engineered antibody that binds to CD20 on mature B cells, including certain lymphoma cells. *See* Ex. 1002 ¶ 41; Pet. 18; Ex. 1017 at 1;

Ex. 1018 at 7. After binding, rituximab causes the patient's own immune system to target these cells for destruction. *Id.*

Rituximab was initially approved by the FDA in November 1997 as monotherapy to treat patients with relapsed low-grade NHL. *See* Pet. 3. It was the first approved anti-cancer monoclonal antibody; the field of immunotherapy was developing and unexplored at the time of the priority date. *See* Ex. 2006 at 2.

III. U.S. PATENT NO. 9,504,744

A. Concurrent and Day 1 Administration of Rituximab and CHOP (Claims 11-12, 15-16)

Independent Claim 11 is directed to the treatment of elderly patients with DLCL using rituximab and CHOP wherein the two agents are administered "concurrently." Independent Claim 12 is similarly directed to the treatment of elderly patients with DLCL using rituximab and CHOP, but requires that rituximab is administered on "Day 1 of each chemotherapy cycle and the CHOP is administered on Day 1 of each chemotherapy cycle." Ex. 1001 at 9:14-15. Claim 15 depends on Claim 12 and further requires that the dose of rituximab given is 375 mg/m^2 and that six or eight chemotherapy cycles are administered. Claim 16, which depends on Claim 15, requires that eight chemotherapy cycles are administered.

B. CHOP and Rituximab In Combination With Transplantation (Claims 1-10, 13-14)

Independent Claim 1 (and therefore dependent Claims 2-10, 13-14 as well) requires administration of CHOP, and an anti-CD20 antibody, wherein the anti-CD20 antibody is administered in combination with stem cell transplantation, to treat elderly patients with DLCL. Claims 7, 9, 13-14 further require that rituximab and CHOP are administered concurrently (Claim 7) or both on Day 1 (Claims 9, 13-14).

C. Prosecution History

During prosecution, Patent Owner overcame an obviousness rejection based on two of the references in Petitioner's Grounds: Link (Ex. 1005) and Coiffier (Ex. 1007). *See* Ex. 1028.

Patent Owner distinguished Link by explaining that it taught administering rituximab and CHOP on different days, not concurrently or both on Day 1. *See* Ex. 1028 at 6. Patent Owner also distinguished Link on the basis that it "does not disclose treating elderly (>60 year old) DLCL patients." *Id.*

Patent Owner distinguished Coiffier because it taught "treatment with rituximab as a single agent, and expressly excluded combination treatment with chemotherapy and corticosteroids such as prednisone." *Id.* at 6-7, citing Ex. 1007 at 2 ("Treatment with corticosteroids or other chemotherapeutic agents was not permitted.").

Patent Owner explained that "the art prior to August 1999 taught away from combining rituximab and CHOP to treat elderly patients (>60 years old)," and that "[a]t that time, even CHOP alone was thought to perhaps be too toxic for certain elderly patients." Ex. 1028 at 7. "It had been reported that the percentage of toxic deaths in elderly patients treated with full dose CHOP increased dramatically." *Id*. (citing Ex. 1007 at 873). Patent Owner further explained that the POSA would not have known whether the combination of rituximab and CHOP would be safe and effective in elderly patients, or "whether the combination would reduce the efficacy that would otherwise be achieved with rituximab or CHOP alone." *Id* at 8.

Petitioner argues that "the only stated reason for allowing the claims was that the Applicants incorporated 'in combination with a transplantation regimen' into claim 1." Pet. 27. But that is plainly incorrect. For example, the "concurrent" and "Day 1" group of claims (Claims 11-12, 15-16) do not even have a "transplantation" limitation. The examiner allowed those claims because none of the art taught giving rituximab and CHOP concurrently or both on Day 1.

IV. CLAIM CONSTRUCTION

A. "in combination with a transplantation regimen" (Claims 1-10, 13-14)

A POSA would have understood the phrase "in combination with stem cell transplantation regimen" to mean that "*during* a stem cell transplantation regimen."

1. The Specification Describes The Invention As Administering The Anti-CD20 Antibody "During Bone Marrow Or Stem Cell Transplant."

"[C]laims should always be read in light of the specification and teachings in the underlying patent." *D'Agostino v. MasterCard Int'l*, 844 F.3d 945, 948 (Fed. Cir. 2016).

The specification states that "rituximab can be administered at induction, in vivo purging, mobilization, conditioning, post-transplant reinfusion and at any other time *during bone marrow or stem cell transplant* for the purpose of improving the survival rate of transplant recipients."[4] Ex. 1001 at 6:28-33. A POSA would have understood this to be teaching that the anti-CD20 antibody is administered at any time during stem cell transplantation, including at the listed times—or any other time—during a transplantation regimen.

"The present invention," the specification states, "includes administering anti-CD20 antibodies…*as part of a transplant regimen*…." Ex. 1001 at 2:38-44. As Dr. Ozer previously testified, "[a] person having ordinary skill in the art would have understood that administering anti-CD20 antibodies as part of a transplant

[4] The '744 patent describes each of the terms in this list. Ex. 1001, 6:17-53.

regimen means administering the antibodies during the transplant regimen"—"[a]t any point in the transplant." Ex. 2002 at 66:8-12.[5]

Additionally, the specification states: "Thus, with rituximab treatment *at the various stages of transplantation*, marrow may be harvested prior to myeloablative radiotherapy, and reintroduced subsequent to such therapy…." Ex. 1001, 7:3-6. A POSA would have understood that rituximab treatment "at the various stages of transplantation" refers to rituximab treatment during the transplantation regimen.

Accordingly, the specification indicates that administering an anti-CD20 antibody in combination with a stem cell transplantation regimen means administering the anti-CD20 antibody during one of the stages of stem cell transplantation, such as during an induction, in vivo purging, mobilization, or conditioning stage. Ex. 1001, 6:28-33.

2. Petitioner's Expert Opinion.

Petitioner's expert Dr. Ozer opined that the claim language "includes, but is not limited to, the administration of the anti-CD20 antibody (e.g., rituximab) *before* stem cell transplantation." Ex. 1002 ¶ 78 (emphasis in original). For support, Dr. Ozer cites portions of the specification describing the use of rituximab during induction, in vivo purging, mobilization, conditioning, or at any other time

[5] As noted above, this deposition occurred in an IPR for the parent patent, U.S. No. 8,821,873, which shares the same specification as the '744 patent.

during a transplantation regimen. *Id.* ¶ 80-82. Dr. Ozer does not appear to be taking the position that rituximab can be administered outside the claimed "transplantation *regimen*," which may include stages of induction, in vivo purging, mobilization, etc. As Dr. Ozer confirmed, "before harvesting, a stem cell transplantation regimen could include an in vivo purging stage." Ex. 2002 at 37:19-23. "Alternatively, a stem cell transplantation regimen could include a mobilization stage." *Id.* at 37:24-38:3. Dr. Ozer's testimony is consistent with Patent Owner's proposed construction.

For avoidance of doubt, Patent Owner's proposed construction would exclude patients who received rituximab only as part of first-line treatment with CHOP, subsequently relapsed, and then received a transplantation regimen that did not include rituximab. As discussed above, the claims require that rituximab is given *during* a transplantation regimen.

B. "CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone) chemotherapy"

For purposes of deciding whether to institute trial, the Board does not need to construe this term because Petitioner's Grounds fail even under Petitioner's proposed construction.

C. "diffuse large cell lymphoma"

For purposes of deciding whether to institute trial, the Board does not need to construe this term because Petitioner's Grounds fail even under Petitioner's proposed construction.

D. "concurrently"

Patent Owner disagrees with Petitioner's proposed construction of "'concurrently' as requiring the infused drugs in the claimed combination therapy to be administered on the same day during the same hospital visit." Pet. 30. For purposes of deciding whether to institute trial, however, the Board does not need to construe the term because Petitioner's Grounds fail even under Petitioner's proposed construction.

V. GROUND I — PETITIONER FAILS TO ESTABLISH A REASONABLE LIKELIHOOD THAT CLAIMS 11-12, 15-16 ARE OBVIOUS

To prove obviousness, Petitioner must show "that a skilled artisan would have had 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." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012). Obviousness "cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention."

Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., 725 F.3d 1341, 1352 (Fed. Cir. 2013).

Each of claims 11-12 and 15-16 requires treating elderly patients with DLCL using rituximab and CHOP, wherein rituximab and CHOP are given concurrently or both on Day 1 of each chemotherapy cycle. Petitioner fails to establish that a POSA would have been motivated to administer an anti-CD20 antibody and CHOP that way, or would have had a reasonable expectation of success in doing so.

A. No Motivation To Administer Anti-CD20 Antibody and CHOP Concurrently Or Both On Day 1 (Claims 11, 12, 15, 16)

None of Petitioner's references discloses administering CHOP and rituximab concurrently or both on Day 1. On the contrary, the references only taught administering rituximab and CHOP on different days.

1. The Alleged Prior Art Only Taught Administering Rituximab And CHOP On Different Days

Petitioner recognizes that its primary reference, Link (Ex. 1005), taught administering rituximab to patients two days prior to CHOP each cycle. *See* Pet. 44. Patients "received six cycles of therapy" with "rituximab 375 mg/m^2 on day 1 of each 21 day cycle followed 48 hours later by CHOP." Ex. 1005 at 7. Rituximab and CHOP were not administered concurrently or both on Day 1. *Id.*

Petitioner neglects to mention another clinical study it was aware of that disclosed a dosing regimen for rituximab and CHOP. That study, conducted by

Dr. Myron Czuczman and others, also administered rituximab and CHOP on different days.[6] An abstract of the Czuczman study reported that rituximab and CHOP were given using a staggered dosing regimen. Ex. 2007 at 11 (reporting that "IDEC-C2B8" [rituximab] and "CHOP" were administered on different weeks).

The final results of the Czcuzman study were published in a full article in early 1999 (before the priority date). *See* Ex. 2001 (library date stamped with received date of April 23, 1999). In the full article, the authors provided a detailed explanation of the benefits of administrating rituximab and CHOP on different days, contradicting Petitioner's assertion that "it [was] obvious based on the general knowledge of a POSA to administer rituximab and CHOP chemotherapy concurrently." Pet. 44.

[6] Petitioner's omission is telling, not only because this is the only reference other than Link that disclosed a dosing regimen for rituximab and CHOP, but also because Petitioner relied on this Czuczman study in another IPR against a different patent in Patent Owner's rituximab portfolio. In *Pfizer v. Biogen*, IPR2018-00186, the Petitioner relied on a 1995 abstract reporting interim results from this Czuczman study. *See* Ex. 2008 (IPR2018-00186 Petition) at 15, citing Ex. 2007 (an abstract publication of the Czuczman study identified as "Exhibit 1004" in that Petition).

In the Czuczman study, rituximab was given as pretreatment before CHOP, intermittent doses between cycles, and also as "mop up" doses after the last cycle:

> Rituxan infusions 1 and 2 were administered on days 1 and 6 before the first CHOP cycle, which started on day 8. Rituxan infusions 3 and 4 were given 2 days before the third and fifth CHOP cycles, respectively, and infusions 5 and 6 were given on days 134 and 141, respectively, after the sixth CHOP cycle.

Ex. 2001 at 270.

The Czuczman article explains that rituximab and CHOP were given on separate days because (1) pre-treatment with rituximab was known to sensitize cancer cells to chemotherapy, (2) expected synergy with interim dosing of rituximab, and (3) post-chemotherapy doses of rituximab were used to "mop up" residual cancer cells:

> This mAb schedule was chosen to take advantage of three different characteristics of Rituxan in addition to its known clinical activity in NHL: (1) in vitro data demonstrating its ability to sensitize chemoresistant cell lines; therefore, doses 1 and 2 could be viewed as a form of induction immunotherapy that could possibly render chemoresistant cells chemosensitive; (2) in vitro data demonstrating that possible synergy with cytotoxic agents would best be effected by interim doses 3 and 4; and (3) the generally well-accepted belief that

> monoclonal antibodies are extremely effective in a minimal residual disease setting thus, doses 5 and 6 could be viewed as being used as a ‘‘mop up’’ of residual lymphoma after completion of systemic chemotherapy.

Id. at 270. The study authors also explained, after the priority date, that an additional reason for separating the administration was "[t]o limit the possibility of additive toxicities." Ex. 2009 at 9. Each of these clinical reasons for staggering the administration of rituximab and CHOP were well-supported by other literature in the art.

Thus, before the priority date, the only disclosures of administering rituximab and CHOP taught administering them on separate days. As explained by the Czuczman study authors, they staggered administration of rituximab and CHOP for efficacy reasons. Petitioner has failed to establish that a POSA would have ignored these teachings and administered rituximab and CHOP concurrently or both on Day 1.

2. A POSA Would Not Have Administered Rituximab And CHOP On The Same Day Due To Efficacy Concerns

A POSA would have known that only staggered administration of rituximab and CHOP had been shown to be efficacious with tolerable toxicity, and that there were strong scientific reasons for using staggered administration.

a. *Only Pretreatment With Rituximab Could Sensitize Cancer Cells To The Doxorubicin In CHOP*

A POSA would have known that *in vitro* studies showed that pretreatment with rituximab sensitized cancer cells to certain chemotherapy drugs, including doxorubicin (a.k.a. "hydroxydaunorubicin" or "H") in CHOP, and by doing so, increased the likelihood of effectively treating the cancer.

As discussed above, the Link and Czuczman studies administered rituximab as pretreatment—days before CHOP was administered. The Czuczman authors expressly wrote that the purpose of pretreatment was to sensitize the cancer cells to CHOP chemotherapy, as supported by *in vitro* synergy data at the time. *See* Ex. 2001 at 4 ("in vitro data demonstrating its ability to sensitize chemoresistant cell lines; therefore, doses 1 and 2 could be viewed as a form of induction immunotherapy that could possibly render chemoresistant cells chemosensitive."). Similarly, the Link study investigators also administered rituximab pretreatment for the purpose of sensitizing the cancer cells for CHOP therapy. *See* Ex. 2002 at 50:10-14 (testifying that the Link discussion of synergy was based on "in vitro studies show[ing] that Rituximab's [sic] pretreatment of cancer cells sensitized the cells to cytotoxicity from certain chemotherapies"); Pet. 20.

The *in vitro* synergy data informing the rituximab pretreatment regimens used in Link and Czuczman was published in 1997 in a paper by Professor Aicha Demidem (Ex. 1033). *See* Ex. 2001 at 3, citing Ex. 1033. This Demidem study

found that rituximab (a.k.a. "C2B8") pretreatment sensitized the cancerous "B cell line DHL-4" to doxorubicin, thereby increasing effectiveness of doxorubicin. *See* Ex. 1033 at 2 ("While the DHL-4 [cancer cells] were relatively resistant to several cytotoxic drugs, ***pretreatment*** with C2B8 rendered the cells sensitive to…adriamycin….").

Petitioner relies on the Demidem article (Ex. 1033), *see* Pet. 43, but omits the study's critical finding that in order for rituximab to sensitize cancer cells to doxorubicin (brand name Adriamycin), pretreatment with rituximab "needed" to occur days before chemotherapy was administered, *i.e.*, ***not*** on the same day. *See* Ex. 1033 at 6 ("Time kinetics of C2B8 antibody treatment revealed that sensitization of DHL-4 varied with the cytotoxic agent used namely 4-5 days were needed for DTX, ADR [Adriamycin] and CDDP whereas 2 days were sufficient for ricin….").

Based on the teachings of Link and Czuczman, which relied on, and cited, the *in vitro* study of Demidem, a POSA would have understood that pretreatment with rituximab (not same day administration) was needed to sensitize cancer cells to CHOP. This is why the clinicians of Link and Czuczman administered rituximab as pretreatment days before CHOP cycles in order to provide patients a better chance of treating their cancer.

b. *Chemotherapy Weakens The Aspects Of The Immune System On Which Rituximab Relies To Destroy B Cells*

A further reason to avoid same day treatment with rituximab and CHOP is due to their conflicting activities. Rituximab relies on the patient's own immune system to destroy cancerous B-cells. CHOP, however, was well known to severely weaken a patient's immune system. Staggered administration of rituximab and CHOP alleviated, in part, the concern that CHOP would reduce the ability of rituximab to kill cancer cells.

Petitioner acknowledges that rituximab's ability to deplete B cells was dependent on the patient's immune system. *See* Pet. 18 ("The antibodies [rituximab] can activate the human immune system when they bind to their specific antigens and facilitate the destruction of the cell to which they are bound."). In particular, as explained in Petitioner's cited references, rituximab requires the body's immune processes of complement-dependent cell cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) to destroy cancer cells. *See* Ex. 1018 at 7 ("Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cell mediate cytotoxicity (ADCC).").

Components of CHOP, however, were known to weaken a patient's immune system and to deplete the immune cells necessary for proper ADCC function. For example, glucocorticoids, such as prednisone/prednisolone in CHOP, were known

to inhibit ADCC activity. *See* Ex. 2010 at 17 ("Glucocorticoids inhibit NK-cell-mediated cytotoxicity and antibody-dependent cellular cytotoxicity (ADCC)."). In fact, the literature specifically warned that "steroids could compromise the efficacy of rituximab via their effects on host effector cells." Ex. 2006 at 3. Due to the concern that glucocorticoids could interfere with rituximab's activity, glucocorticoids were excluded from the pivotal rituximab monotherapy clinical trial in 166 patients. *See* Ex. 1031.

Similarly, other components of CHOP were known to deplete the immune cells necessary for proper ADCC function, thereby also reducing the effectiveness of rituximab. A POSA would have been aware that CHOP therapy reduces the number of white blood cells (a.k.a. leukocytes), including neutrophils, lymphocytes, natural killer cells, and monocytes. *See* Ex. 2011 at 7 (showing that CHOP resulted in severe leucopenia in 45% of patients; and severe neutropenia in 51% of patients); Ex. 2012 at 6 (showing 73% incidence of severe leukopenia); Ex. 2002 at 33:12-17 (agreeing that CHOP causes "leukopenia…[t]hat includes neutrophils, lymphocytes, natural killer cells and monocytes").

These immune cells depleted by CHOP, however, are necessary for proper ADCC function. *See* Ex. 2013 at 1 ("It is well known that neutrophils are capable of mediating antibody-dependent cellular cytotoxicity (ADCC) against tumour cells…."); Ex. 2014 at Abstract ("The three major immunocompetent cells in

human peripheral blood (lymphocytes, neutrophils, and monocytes) were shown to be effector cells for antibody-dependent cell-mediated cytotoxicity (ADCC)….").

A POSA would have been concerned, therefore, that same day administration of rituximab and CHOP would reduce the efficacy of rituximab. In order to alleviate that concern, as much as possible, a POSA would have given rituximab on different days than CHOP—like the clinicians in Link and Czuczman did with their staggered administration regimens that administered rituximab pretreatment before CHOP.

c. *Administering Rituximab After CHOP Mops Up Minimal Residual Disease*

A further reason for administration of rituximab and CHOP on different days, where rituximab follows CHOP therapy, is that rituximab was thought to be more effective in a minimal residual disease setting, *i.e.*, after CHOP reduced the disease tumor burden.

In the Czuczman study, the last two doses of rituximab were given approximately 2-3 weeks after the final CHOP cycle. *See* Ex. 2001 at 270. The authors explained that these last rituximab doses were designed to "mop up" residual lymphoma, and that there was a "generally well accepted belief that monoclonal antibodies are extremely effective in a minimal residual diseases

setting."[7] *Id; see also* Ex. 1009 at 10 (explaining that rituximab could be used "following standard chemotherapy in an attempt to decrease minimal residual lymphoma"). Rituximab was thought to be "extremely effective in a minimal residual diseases setting" because the reduced tumor burden allows for more rituximab to bind per cancer cell; thereby increasing the likelihood of lysis. As Dr. Ozer testified, "the more rituximab antibodies bound to the cell the more likely that cell will be destroyed." Ex. 2002 at 40:23-41:2. If, on the other hand, rituximab was given on the same day as CHOP chemotherapy, then much of the rituximab would have bound cancer cells that are killed by the chemotherapy drugs, leaving less rituximab to bind cancer cells remaining in the minimal residual disease setting.

Petitioner fails to show that a POSA would have been motivated to give rituximab and CHOP concurrently or both on Day 1 when, to the contrary, clinicians had administered rituximab doses weeks after the last CHOP cycle as "mop up" to provide patients a better chance of treating their cancer.

[7] "Minimal residual disease" refers to nearly undetectable amounts of cancer cells that may remain in the body of a NHL patient after treatment.

3. A POSA Would Not Have Administered Rituximab And CHOP On The Same Day Due To Toxicity Concerns

A POSA also would have staggered treatment to avoid the additive toxicities of rituximab and CHOP, as in the Czuczman study. Ex. 2009 at 9 (explaining that "[t]o limit the possibility of additive toxicities, rituximab and the CHOP regimen were administered on different days.").

As of the priority date, rituximab was still a novel, first-in-class drug. The risks associated with monoclonal antibodies, and rituximab in particular, were only beginning to be understood.[8] FDA approval was limited to monotherapy administration in LG-NHL. Ex. 1018 at 10. And while results from the monotherapy LG-NHL studies may have indicated that rituximab was a relatively tolerable drug overall, it was not without its toxicities. In particular, studies showed that rituximab was associated with high incidence of infusion reactions, especially "during the first infusion." *See* Ex. 1031 at Abstract; *id.* at 6 ("Adverse events

[8] Since Rituximab was first approved in November 1997, there have been several warnings added to the label, including Black Box Warnings for "fatal infusion reactions, severe mucocutaneous reactions, hepatitis B virus reactivation, and progressive multifocal leukoencephalopathy." *See* Ex. 1034, Current Rituxan label at 1.

generally occurred during therapy or within the first 30 days following therapy."); *id.* at 6 (identifying frequency of adverse events, including infusion reactions).

Similarly, CHOP chemotherapy was also known to be associated with toxicity during administration. *See* Ex. 2011 at 7 (reporting that 73% of patients treated with CHOP had at least one "severe adverse experience," such as infection, leucopenia and neutropenia). As Petitioner's expert testified, for example, hypersensitivity reactions to CHOP occur most frequently during the first administration. *See* Ex. 2002 at 35:21-25; *see also* Ex. 2015 at Abstract (reporting that "the onset of the [hypersensitivity] reaction coincided with the initiation of the doxorubicin").

Clinicians administered rituximab and CHOP "on different days" to avoid additive toxicities. *See* Ex. 2009 at 9 (explaining that "rituximab and the CHOP regimen were administered on different days" "[t]o limit the possibility of additive toxicities."). The regimens used by clinicians in Link and Czuczman that administered rituximab and CHOP on different days provided a so-called "wash out" period between administrations, thereby allowing the clinician to carefully monitor for toxicity following treatment with rituximab or treatment with CHOP chemotherapy. Only the staggered treatment regimens used in Link and Czuczman had been shown to have tolerable toxicity as of the priority date. There was no

clinical safety data regarding the toxicity of administration of rituximab and CHOP on the same day.

Moreover, there was no clinical data on whether rituximab and CHOP were tolerated in DLCL patients >60 years old, who experienced "more severe treatment related toxicity" (*see* Ex. 1004 at 4; Section II.A.3), even with staggered administration, let alone concurrent administration. Put simply, there was no motivation for a POSA to put elderly DLCL patients at greater risk of toxicity by administration of rituximab and CHOP on the same day.

Additionally, according to Petitioner's own reference, whenever clinicians combined CHOP with one or more other drugs, hereinafter "CHOP-plus" regimens, they did so by administering different drugs on separate days. None of these CHOP-plus regimens gave all the additional drugs concurrently or on Day 1 with the components of CHOP. For example, in the regimen known as COP-BLAM (which adds procarbazine and bleomycin to the components of CHOP), the cyclophosphamide, doxorubicin, and vincristine are given on day 1, the procarbazine and prednisone are given on days 1-10, and the bleomycin is given on day 14. *See* Ex. 1014 at 43. As another example, in the regimen known as ProMACE/CytaBOM (which adds etoposide, cytarabine, bleomycin, methotrexate, leacovorin, and cotrimoxazole to the components of CHOP), the cyclophosphamide, doxorubicin, and vincristine are given on day 1, the cytarabine,

bleomycin, vincristine, and methotrexate are given on day 8, the leacovorin is given on day 9, prednisone is given on days 1-14, and cotrimoxazole is given daily. As a final example, in the regimen known as "EPOCH" (which adds etoposide to the components of CHOP), the drugs etoposide, vincristine, and doxorubicin were given on days 1-4, prednisone was given on days 1-6, and cyclophosphamide was given on day 6. *See* Ex. 2016 at 2.

Petitioner fails to show that a POSA would have been motivated to administer rituximab and CHOP concurrently or both on Day 1 with CHOP when ***no*** other CHOP-plus regimen administered all the components concurrently or all on Day 1.

4. Petitioner Fails To Establish That A POSA Would Have Been Motivated By Convenience and Cost To Administer Rituximab And CHOP Concurrently Or Both On Day 1

None of the five references in Petitioner's Grounds (or any other reference cited by Petitioner) teaches administering rituximab and CHOP on the same day. And as discussed in the preceding Section, every clinical reference evaluating rituximab and CHOP as of the priority date administered rituximab and CHOP on different days. Petitioner was aware of each of these studies, but fails to explain why a POSA would have ignored these teachings to administer rituximab and CHOP on different days to treat a fatal cancer such as DLCL. Petitioner instead resorts to hindsight to argue that a POSA would have been motivated to administer

rituximab and CHOP on the same day based on (1) "general knowledge of a POSA" and (2) "convenience to both doctors and patients." Pet. 44. Neither argument withstands scrutiny.

Petitioner first argues that it was "general knowledge" to administer rituximab and CHOP concurrently "to maximize the amount of time the half-lives of the drugs overlapped," relying exclusively on its expert declaration. *See* Pet. 44 (citing Ex. 1002 ¶ 100, which contains no citations of its own). Petitioner's "assertion, however, is conclusory, and relies exclusively on [its expert] declaration testimony, which merely repeats the conclusory statements in the Petition without citation to any prior art references or any other evidence." *C.R. Bard v. Medical Components*, IPR2015-01660, Paper 9, at 11 (Feb. 9, 2016). Both Petitioner's and its expert's conclusory, unsupported assertions must be rejected. *Id.*; *see also Pfizer v. Biogen*, IPR2017-01167, Paper 9 at 6-7 (previously finding that "Dr. Ozer has not identified any discussion in [a reference] to support that reasoning, or referred us to any other evidence to support that assertion" and therefore, "[w]ithout more, we do not accord persuasive weight to Dr. Ozer's opinion").

In any event, Petitioner's argument is contradicted by the evidence. As discussed in Section 2, maximizing overlapping half-lives was ***not*** desirable for efficacy and toxicity reasons. To the contrary, the only clinical studies

administering rituximab and CHOP administered the drugs on different days for efficacy and toxicity reasons. *See* Section 2.

Based again on alleged "general practice and knowledge," Petitioner argues that a POSA would have administered rituximab and CHOP concurrently "for the convenience to both doctors and patients by aligning treatments for fewer hospital visits." Pet. 44. According to Petitioner, "it was a general practice to try to reduce the number of outpatient visits because of the high cost associated with such visits to the patients." *Id*. For this argument, Petitioner relies on two articles (Exhibits 1035 and 1036)—neither of which is part of Grounds I or III. Neither reference supports Petitioner's arguments.

Petitioner cites Exhibits 1035 (Houts) and 1036 to argue that nonmedical costs are paid out-of-pocket and can be a financial hardship. Pet. 44-45. Exhibit 1036 is a review article that simply cites Houts for the amount of nonmedical costs. *See* Ex. 1036 at 4. Petitioner's increase-in-cost argument, therefore, is entirely based on Houts. But while Houts discusses non-medical costs of hospital visits, the article does not conclude or even suggest that such costs can be reduced by giving all the chemotherapy agents on the same day. *See generally* Ex. 1035. It is therefore not surprising that when the Petitioner and its expert reach the key issue—whether the "cost [of out-of-pocket expenses and wages lost] would have increased substantially with an additional outpatient visit for each cycle"—

there is no supporting citation to any evidence for this argument. *See* Pet. 45, *citing* Ex. 1002 ¶ 101. Such unsupported testimony should be rejected. *See C.R. Bard, Inc.*, IPR2015-01660, Paper 9, at 11.

In fact, Houts reports only a modest difference of $27 in out-of-pocket expenses and wages lost for a treatment ***week*** versus a non-treatment ***week*** during the course of therapy. Ex. 1035 at 1. But as discussed in Section V.A.1, while the Link study staggered the administration of rituximab and CHOP, the two were nonetheless given in the ***same*** week. Houts, therefore, does not support Petitioner's argument that there would be cost savings from administering rituximab and CHOP concurrently compared to what was done in Link. The "treatment week" in Houts, for example, could already encompass multiple clinic visits in a single week, in which case, there would not be more "treatment weeks" for Link's staggered dosing regimen as compared to concurrent administration.

Even assuming there may be some cost savings with concurrent administration, Houts shows that this would not be substantial. In Houts, patients spent on average $73 for out-of-pocket expenses and wages lost during treatment weeks and $46 during non-treatment weeks. That is a difference of only ***$27*** for treatment versus non-treatment weeks. So even assuming that administering rituximab and CHOP on the same day would result in one fewer "treatment week," the saving would not be substantial, contrary to Petitioner's assertion.

Moreover, none of the references cited by Petitioner addresses convenience or costs of administering rituximab or CHOP in particular. This gap in the evidence is important because if staggered administration of rituximab and CHOP (as done in Link and Czuczman) was expected to increase the likelihood of efficacy and tolerable toxicity, as discussed in Section V.A.2, then staggered administration may lead to fewer hospital days overall by preventing disease progression or toxicity-related hospital visits.

In any event, in the context of designing a treatment regimen to cure a life-threatening disease like DLCL, Petitioner has not shown that any alleged convenience or minor cost-savings for the patient outweighed the considerations of greater efficacy and lower toxicity with staggered administration. As Dr. Ozer testified in a related action, "efficacy and toxicity were ***the*** critical parameters for designing a treatment regimen for DLCL patients over 60 years old." Ex. 2002 at 59-60, citing Petitioner's Petition in related IPR2017-01168.

Indeed, as discussed in Section V.A.3, whenever oncologists historically added drugs to CHOP to treat DLCL patients, these "CHOP plus" regimens called for non-concurrent administration even though such regimens may have led to more clinic visits for drug administration.

B. No Reasonable Expectation Of Success For Either Concurrent Or Day 1 Administration Of Rituximab and CHOP In Elderly Patients With DLCL (Claims 11-12, 15-16)

Petitioner also fails to carry its burden to show "that the skilled artisan would have had a reasonable expectation of success." *In re Cyclobenzaprine*, 676 F.3d at 1069. "[I]n the unpredictable arts such as medicinal treatment, for a method to be obvious to try, there must be some suggestion in the prior art that the method would have a reasonable likelihood of success." *In re Efthymiopoulos*, 839 F.3d 1375, 1380 (Fed. Cir. 2016). Petitioner's cited art highlights the unpredictability of successfully treating the claimed elderly patients: "The elderly have a higher relapse rate…and we don't really understand why." Ex. 1006 at 2. This is the antithesis of a reasonable expectation of success.

As discussed in Section V.A, none of the references taught giving rituximab and CHOP concurrently or both on Day 1. To the contrary, clinical trials evaluating the combination of rituximab and CHOP administered rituximab and CHOP on different days—and for good reason, based on what was known in the art about their efficacy and toxicity. *Id.* The prior art, therefore, provided no reasonable expectation of success, either in terms of efficacy or toxicity, for administering rituximab and CHOP concurrently or both on Day 1.

Furthermore, none of the cited references reported actual clinical results for administering rituximab and CHOP together in any manner—*e.g.*, on the same or

different days—in patients greater than 60 years old, for whom toxicity was of particular concern. A POSA would have been even more concerned about the toxicity associated with administering "six or eight," or "eight," cycles of CHOP and rituximab, as required by dependent claims 15 and 16 respectively. Petitioner's expert, in fact, testified in a related IPR that elderly patients are "***unable*** to get in all 6 to 8 cycles of CHOP"—Ex. 2002 at 29:24-30:2; *see also* Ex. 1006 at 1 (teaching that elderly patients "have a hard time getting to six or eight" cycles of CHOP).

Petitioner has failed to show a reasonable expectation of success for administering rituximab and CHOP concurrently or both on Day 1 for elderly patients with DLCL.

1. CHOP Was Known To Be Highly Toxic To Elderly Patients, And The Combination of Rituximab And CHOP Had Not Been Studied In This Population

Before the priority date, as Petitioner's own reference explains, elderly patients had "[i]nferior outcomes" with therapy:

> Inferior outcomes [for elderly patients] may result from differences in disease biology, with more frequent relapses from a remission state, use of lower doses of chemotherapy, which results in poorer disease control, increased susceptibility to the toxic effects of chemotherapy and more treatment-related deaths, and an

> increased prevalence of comorbid conditions, with more deaths from causes unrelated to lymphoma.

Ex. 1004 at 4.

Those skilled in the art were greatly concerned that CHOP chemotherapy, even by itself, was highly toxic in elderly patients. *See* Ex. 1006 at 1 ("CHOP…is more toxic in this age group"); Ex. 1004 at 3 (reporting "more severe treatment related toxicity" for elderly patients); Ex. 1016 at 10 (explaining that in elderly NHL patients, "toxicity may be enhanced, [and] many physicians believe that elderly patients are unable to withstand intensive chemotherapy"); Ex. 2002 at 31:6-8 (agreeing that "CHOP was known to cause more adverse events in patients greater than 60 years old.").

Studies showed that elderly patients receiving CHOP experienced high rates of hospitalization for serious adverse events. Ex. 1004 at 10 ("Sixty-three percent of [elderly] patients treated with CHOP were admitted to hospital at least once, and 47% had at least one admission for management of fever while neutropenic. This rate of hospitalization indicates that elderly patients are susceptible to the toxic effects of full-dose CHOP.").

The high toxicity rate in elderly patients was attributed to the presence of concomitant conditions and increased sensitivity to drug side effects. Ex. 1020 at 2. Elderly patients also "have changes in liver and kidney functions that may alter drug metabolism; moreover, they may have a reduced bone marrow reserve and

may have metabolic and cardiovascular diseases." Ex. 1013 at 10. "As a consequence, because toxicity may be enhanced, many physicians believe that elderly patients are unable to withstand intensive chemotherapy . . . ." *Id.*; *see also* Ex. 2017 at 4 (explaining that elderly patients metabolized and responded to chemotherapy differently, with particular concern for "exaggerated drug toxicity").

Moreover, a POSA would have been concerned with the potential ability of chemotherapy drugs, including the cyclophosphamide component of CHOP, to "induce or exacerbate heart failure." Ex. 2018 at 1-3. A POSA would have been aware of numerous reports on both "reversible and irreversible heart failure[,] indicat[ing] a wide spectrum of cyclophosphamide-induced cardiotoxicity," including severe hypotension. *Id.* at 3; *see also* Ex. 2019 at Summary (reporting incidence of "grade III acute cardiomyopathy and hypotension" induced by cyclophosphamide).

Before the priority date, a POSA would have known that rituximab was also associated with cardiac hypotension and arrhythmia. *See* Ex. 1031 at 6. And in light of knowledge in the art that cyclophosphamide was cardiotoxic—perhaps more so in elderly patients (>60 years old)—a POSA would not have had a reasonable expectation of success for a regimen of rituximab and CHOP in elderly patients with DLCL.

Apart from toxicity, efficacy of rituximab and CHOP in the population of DLCL patients greater than 60 years old was also uncertain. Results with rituximab were decidedly less impressive in patients with intermediate-grade NHL than in those with low-grade NHL. *See* Ex. 2020 at 12 (reporting rituximab's success rates in treating LG-NHL but noting lack thereof in IG-NHL patients: "The response data in intermediate and aggressive histologies to date have been less impressive"); *id.* at 10 (describing Coiffier's results as "suggest[ing] that even with prolonged treatment with rituximab, intermediate- and high-grade lymphomas respond less favorably to anti-CD20 therapy"). Moreover, the art recognized that the claimed elderly patient population responded to cancer therapy unpredictably, and researchers "d[id]n't really understand why" (Ex. 1006 at 2)—the polar opposite of circumstances leading to any reasonable expectation of success.

Against this backdrop, it was surprising and remarkable that the inventors of the '744 patent called for administering to patients a chemotherapy believed to be unduly toxic in the elderly and an antibody shown to be ineffective in intermediate-grade NHL to create a safe and effective treatment for elderly DLCL patients.

2. Link Did Not Study Elderly Patients, Nor Report Results For Enrolled DLCL Patients As A Group

Petitioner primarily relies on Link (Ex. 1005) to argue that a POSA would have expected rituximab and CHOP to have tolerable toxicity in the claimed elderly patients with DLCL. *See* Pet. 35. But Link did not study elderly patients.

Link is an abstract of a phase II, open-label pilot study of rituximab and CHOP in IG/HG-NHL patients, including patients with IWF type "D", "G," and "H" pathologies. Ex. 1005 at 7. Link treated thirty-one patients, thirty of whom were evaluable. *Id.* The abstract does not report results for the type "G" patients, *i.e.*, DLCL patients, as a group. It simply reports overall results across all groups of 19 complete responses, 10 partial responses, and one patient with progressive disease. *Id.*

Thirteen patients in the Link study experienced Grade 4 neutropenia, *id.*, a life-threatening disorder requiring immediate intervention. Ex. 2021 at 5 (defining Grade 4 toxicity as a "life threatening or disabling adverse event."). At least Grade 3 neutropenia was observed in connection with more than 20% of the cycles administered, and fourteen patients experienced other Grade 3 toxicities. Ex. 1005 at 7. Patients experienced Grade 1 and 2 toxicities as well. *Id.*

As Petitioner admits, "Link did not study patients over 60." Pet. 20. At the time of invention, a person having ordinary skill in the art knew that age was a critical prognostic factor for NHL. Ex. 1006 at 1. In fact, as noted above, an international study of prognostic indicators in NHL had recently found "that age—being over age 60—was the most important factor independently associated with poorer survival in patients with IG/HG lymphoma." *Id.* Accordingly, a person having ordinary skill in the art would have found the absence of any disclosure of

treating patients >60 years old, let alone a patient >60 years old with DLCL, significant.

Moreover, patients in the Link study received "rituximab 375 mg/m^2 on day 1 of each 21 day cycle followed 48 hours later by CHOP." Ex. 1005 at 7. The results of Link, therefore, do not address the efficacy and toxicity of administering rituximab and CHOP concurrently or both on Day 1, as discussed in Section V.A.

Petitioner argues that "Link taught that adding rituximab to full-dose CHOP was likely more effective in DLCL patients than full-dose CHOP alone, but without additional toxicity." Pet. 19. Link, however, cannot bear the weight of Petitioner's assertion. Link did not use a control group of patients receiving CHOP alone as a comparator. Ex. 1005 at 7. The authors, therefore, could only conclude that the rituximab and CHOP "regimen represents a tolerable therapy with serious adverse events occurring with a frequency similar to that seen with conventional CHOP therapy alone and ***may*** offer higher response rates." *Id*. Stating that a therapy "may" offer higher response rates is far different from stating that a therapy "was likely more effective," as Petitioner alleges.

In any event, Link did not study elderly patients. Pet. 20. Nor did it administer rituximab and CHOP concurrently or both on Day 1. Link, therefore, does not provide a reasonable expectation of success for the claimed invention.

3. McNeil Reports Only The Commencement Of A Study And Articulates No Expectation About The Outcome

McNeil is a news article entitled "Non-Hodgkin's Lymphoma Trials In Elderly Look Beyond CHOP." Ex. 1006 at 1. McNeil discloses that "[r]esearchers in December launched a new randomized trial[,] . . . a phase III trial [that] will compare CHOP alone to CHOP plus the new monoclonal antibody IDEC-C2B8 (Rituxan)," Ex. 1006 at 1, but provides no details about the study design, including the histology of the cancers being studied,[9] the dose of rituximab used, or how many cycles of CHOP would be used. *Id.*

The fact that a study was about to begin would not have provided a reasonable expectation of success, especially when little detail about the study was disclosed. *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).

Moreover, McNeil recognized the unpredictability and lack of success of various therapies in treating the elderly population. *See* Ex. 1006 at 2 (explaining that the elderly-patient population responded to therapy unpredictably, and researchers "d[id]n't really understand why"); *id.* at 1 (explaining that "[o]ne

[9] McNeil states only that the patients would have IG/HG lymphoma, but does not disclose whether any patient would have DLCL in particular. Ex. 1006 at 1.

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 six to eight [cycles]."); *id.* ("CHOP . . . is more toxic in this age group.").

McNeil's disclosures about the difficulties in treating elderly patients show that a POSA would have been pessimistic about successfully treating these patients. *See In re Brimonidine Patent Litig.*, 643 F.3d 1366, 1376 (Fed. Cir. 2011) (where prior art recognizes significant "roadblocks" 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); *DePuy Spine, Inc. v. Medtronic Sofamor Danek. Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009) (a POSA would not "look past [the reference's] warning" and "expresses concern for failure").

McNeil offers no predictions regarding whether the clinical trial it alludes to would be successful. Trials in difficult patient populations often fail. *See* Ex. 2022 at 9 (showing that oncology trials are the least likely of all to be successful, as defined by advancement to next phase of approval process). As Dr. Ozer testified in a related proceeding, these trials often show negative results. *See* Ex. 2002 at 26:15-23 (agreeing that potential therapies "often have negative results in clinical trials" because "[e]ither a combination or a drug that is intolerable or a

combination or a drug that has no efficacy or a combination or a drug that has less efficacy than whatever is the standard.").

McNeil answers none of the questions left unaddressed by Link: How would patients >60 years old respond to rituximab and CHOP? How would DLCL patients > 60 years old respond? Was rituximab plus CHOP more efficacious than rituximab alone or CHOP alone? Did rituximab and CHOP have overlapping toxicities in elderly patients with DLCL?

4. Neither Macedo Nor Meyer Studied Rituximab and CHOP, And Neither Suggests That Such A Combination Would Be Successful In Elderly Patients

Neither Macedo nor Meyer fills the gap left by Link and McNeil or otherwise would have provided a POSA with a reasonable expectation of success for administering rituximab and CHOP concurrently in elderly patients with DLCL.

Meyer reports results from a clinical study comparing full-dose CHOP given every 3 weeks versus one-third doses given weekly in elderly patients with IG lymphoma. Ex. 1004 at 4. Elderly patients enrolled had to have "acceptable cardiac, renal, and liver function." *Id.* Of the 38 patients evaluated, only three were able to receive more than six cycles of CHOP. *Id.* at 7. The study ultimately concluded that "weekly [one-third dose] chop is unlikely to be more effective than [full-dose] CHOP, and may produce inferior outcomes." *Id.* at 10.

While the study enrolled patients with different types of IG lymphoma, including "follicular large-cell, diffuse small cleaved-cell, diffuse mixed, diffuse large-cell, [and] immunoblastic lymphoma," Meyer, like Link, does not report efficacy or safety results for DLCL patients as a group. It simply reports overall results across all groups.

Macedo is a short abstract reporting administration of a "mini CHOP" (reduced doses of doxorubicin compared to full-dose CHOP) and radiation regimen to elderly patients with IG/HG-NHL. Ex. 1003 at 3 ("[P]atients received a total of 6 to 8 cycles of mini-CHOP and a consolidation radiation therapy was applied to sites of bulky disease in the limited stages."). Petitioner acknowledges that Macedo's mini-CHOP required "consolidation radiation therapy," Pet. 16, but fails to provide any evidence or analysis supporting a reasonable expectation of success for using rituximab, mini-CHOP, ***and*** consolidation radiation therapy in elderly patients with DLCL. *See, e.g.*, Pet. 3, 20, 36 (arguing that mini-CHOP would have been used but failing to consider whether radiation could be as well). And Petitioner provides no evidence that mini-CHOP can be used in the absence of consolidation radiation therapy.

In any event, the Macedo abstract does not report how many patients were able to receive six or eight cycles of "mini CHOP." Ex. 1003 at 3. Like the Meyer study discussed above, this study enrolled patients with different types of IG/HG

lymphoma, IWF type "H", "G" (i.e., DLCL patients), "F", "E", and "D" pathologies, and the abstract does not report results for DLCL patients as a group. *Id.* Like Meyer and Link, the Macedo abstract simply reports overall results across all groups.

Even assuming that Macedo and Meyer showed that full-dose CHOP and "mini-CHOP" were tolerable for some patients studied, that would not have indicated to a POSA that the claimed regimens of rituximab and CHOP would be tolerable. Neither reference addresses the toxicity of rituximab, let alone the toxicity of rituximab plus CHOP under any regimen, in elderly patients with DLCL. And as Dr. Ozer opined in a related IPR, "it was known that the total level of toxicity could be unacceptable even if each drug has a tolerable toxicity when given individually." Ex. 2002 at 24:19-24. This would be true even if, as Petitioner alleges, the toxicities of CHOP and rituximab did not overlap. *See id.* at 25:15-19 (agreeing that "the total toxicity associated with using multiple drugs together can be too high even if the toxicities of those individual drugs do not overlap").

In any event, neither Meyer nor Macedo mentions adding another cytotoxic drug to CHOP or "mini-CHOP" or "weekly chop," let alone adding a monoclonal antibody, and anti-CD20 antibody, or rituximab in particular. These articles, therefore, answer none of the questions left unaddressed by Link and McNeil.

5. Coiffier Studied Rituximab Monotherapy And Does Not Indicate That The Combination Of Rituximab And CHOP Would Be Successful In Elderly Patients With DLCL

Coiffier does not fill the gaps left by Link, McNeil, Macedo, and Meyer on the reasonable expectation of success for using concurrently administered rituximab and CHOP for elderly patients with DLCL.

Coiffier reports results from a 54-patient open-label clinical trial using rituximab monotherapy to treat patients with "diffuse large B-cell lymphoma (DLCL), mantle cell lymphoma (MCL), or other intermediate- or high-grade B-cell lymphomas," including IWF "subtypes D to H." Ex. 1007 at 1. While the study enrolled elderly patients, Coiffier did not report results for the elderly patients as a group, let alone elderly patients with DLCL. *Id.* at 2-3 (reporting results). The overall response rate was only 31%. *Id.*

Petitioner argues that the "Coiffier reference confirmed that rituximab was safe and effective in DLCL patients over 60, and recommended combining rituximab with chemotherapy in this patient population." Pet. 21. This is incorrect. While Coiffier did enroll some elderly patients, the study 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." Ex. 1007 at 6. Given the overall response rate of only 31%, *id.* at 3, one cannot tell from Coiffier to what extent elderly patients responded to rituximab monotherapy. Dr. Ozer conceded that

"[w]e don't know whether any of those [patients in Coiffier] that were entered who were greater than 60 were in the group who responded." Ex. 2002 at 55:10-15. Nor could one tell from Coiffier to what extent elderly patients with DLCL, if any, responded to rituximab monotherapy.

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 "toxicity" (in patients of all ages). Ex. 1007 at 6. Thus, Coiffier does not support Petitioner's proposed combination of rituximab with "characteristic[ally] toxic" combination chemotherapy, such as CHOP, in elderly patients with DLCL. *Id.* At most Coiffier makes a bare proposal to try rituximab in combination with standard chemotherapy, which as the term is used in the paper, appears to refer to "single-agent" chemotherapy. *See* Ex. 1007 at 5. 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 general guidance" in the art is at most an invitation to experiment).

C. No Reasonable Expectation Of Success For Administering Six Or Eight Chemotherapy Cycles In Elderly Patients (Claim 15)

For the reasons discussed above, the references in Ground I would not have provided a POSA with a reasonable expectation of success in administering rituximab and CHOP concurrently or both on Day 1 to elderly patients with DLCL.

There would have been even less expectation of success for administering a full ***six or eight*** CHOP cycles in these elderly patients, as required by Claim 15. As Petitioner's expert, Dr. Ozer, testified in a related IPR, elderly patients are "***unable*** to get in all 6 to 8 cycles of CHOP." Ex. 2002 at 29:21-30:2; *see also* Ex. 1006 at 1 (teaching that elderly patients "have a hard time getting to six or eight" cycles of CHOP). Because elderly patients are "unable" to get to even six cycles of CHOP, Petitioner has failed to show a reasonable expectation of success for concurrently administering rituximab and six or eight CHOP cycles to elderly patients with DLCL.

D. No Reasonable Expectation Of Success For Administering Eight Chemotherapy Cycles In Elderly Patients (Claim 16)

For the reasons discussed above, the references in Ground I would not have provided a POSA with a reasonable expectation of success for administering rituximab and CHOP on the same day to elderly patients with DLCL.

There would have been even less expectation of success for administering a full ***eight*** CHOP cycles in these elderly patients, as required by Claim 16. Link is the only one of Petitioner's references that reports any clinical results for the combination of rituximab and CHOP, *see* Pet. 35, and Link did "not study patients over 60." Pet. 20. Moreover, Link limited the number of rituximab doses and CHOP cycles to six. Pet. 35. Petitioner fails to cite any reference disclosing the use of rituximab and CHOP for eight cycles in any patient, let alone in elderly patients.

This failure is critical because, as discussed, Dr. Ozer testified in a related IPR that elderly patients are "unable to get in all 6 to 8 cycles of CHOP"—Ex. 2002 at 29:21-30:2; *see also* Ex. 1006 at 1 (teaching that elderly patients "have a hard time getting to six or eight" cycles of CHOP).

Considering that elderly patients are "unable" to get to six or eight cycles of CHOP, and that Petitioner fails to cite any reference teaching eight cycles of rituximab and CHOP even in non-elderly patients, Petitioner has failed to show a reasonable expectation of success for concurrently administering rituximab and ***eight*** CHOP cycles to elderly patients with DLCL.

E. Petitioner Failed To Establish That The Claimed Invention Was One Of A Finite Number Of Identified, Predictable Solutions

With a single sentence, Petitioner makes the conclusory assertion that Claim 11's "concurrent administration was one of a 'finite number of identified, predictable' dosing options for using rituximab in combination with CHOP." Pet. 45-46, *citing* Ex. 1002 ¶ 102 (expert declaration merely repeating the words from the Petition without any supporting citations).

This argument fails at the outset as a matter of law because Petitioner focuses on a single claim element, "concurrent administration" as the dosing option, instead of the invention as a whole. An obvious-to-try analysis must, however, address the invention as a whole. The "question is whether ***the invention*** is an 'identified, predictable solution,'" *Rolls-Royce, PLC v. United Techs. Corp.*,

603 F.3d 1325, 1339 (Fed. Cir. 2010), not whether a single element of a claim would have been obvious. Put simply, contrary to Petitioner's assertion, it is not a binary inquiry of concurrent versus non-concurrent dosing. The "finite number of identified, predictable" options analysis must evaluate all of the available options to treat DLCL patients greater than 60 years old.

Petitioner, however, does not attempt to identify what all of the available options were, let alone establish that the number of available options was "finite" under the case law. As this Board has held, alleging that a claimed invention is drawn from one of a "finite number of predictable solutions" without "sufficient evidence or explanation" justifying that number exposes Petitioner's allegation as "simply a hindsight statement based on the invention described in the [] patent." *Becton, Dickinson v. B. Braun Melsungen AG*, No. IPR2017-01585, Paper 8, at 19-20 (P.T.A.B. Dec. 15, 2017).

Moreover, Petitioner's own references non-exhaustively identify numerous options that should have been considered. For example, as Dr. Ozer testified, "McNeil identifies [] the chemotherapy CIEP in which the less toxic idarubicin and VP16(P) are substituted for CHOP's doxorubicin and vincristine as a potential alternative to CHOP." Ex. 2002 at 43:25-44:4; Ex. 1006 at 2. Dr. Ozer also confirmed that "McNeil identifies the chemotherapy CTVP, cyclophosphamide, tenopside [sic], and pirarubicin as a potential alternative to CHOP." Ex. 2002 at

44:6-9; Ex. 1006 at 2. Moreover, "other chemotherapeutic regimens available at the time of the claimed invention included m-BACOD, ProMACE-CytaBOM, and MACOP-B." Ex. 2002 at 29:5-9; Ex. 1014 at 42-43. In addition to chemotherapy, a POSA would also have known that radiation therapy (like in Macedo), immunotherapies, and bone marrow transplantations, for example, were potential options. *See* Ex. 1014 at 44-46.

Petitioner's argument is also wrong that concurrent administration of rituximab and CHOP was an identified solution. As discussed in V.A, every clinical study administering rituximab with CHOP before the priority date did so using administration on different days. And each of these studies—Link and Czuczman—used ***different*** dosing regimens, suggesting that there were numerous dosing options to consider that do not administer rituximab and CHOP on the same day. *See* Section V.A.1. Moreover, the literature explained why rituximab and CHOP should be administered on different days for efficacy and toxicity reasons. *Id.* Petitioner relies entirely on hindsight to now allege, without any support, that concurrent administration of rituximab and CHOP was one of a smaller number of identified solutions to treat elderly patients with DLCL. It was not.

Petitioner not only failed to establish that the claimed invention was one of a finite number of identified solutions, but also failed to submit any evidence to show that any such solutions were predictable. This alone is fatal because it is

well-established that medicinal treatment is one of the unpredictable arts. *In re Efthymiopoulos*, 839 F.3d 1375, 1380 (Fed. Cir. 2016) ("[I]n the unpredictable arts such as medicinal treatment…").

Moreover, "for an invention to be obvious to try, there must be a finite number of known choices in the prior art, ***and*** a reasonable expectation of success for the choice that is tried." *Hoffman-La Roche Inc. v. Apotex, Inc.*, 748 F.3d 1326, 1340 (Fed. Cir. 2014). Petitioner failed to establish a reasonable expectation of success, as discussed in Section V.B.

VI. GROUND II — PETITIONER FAILS TO ESTABLISH A REASONABLE LIKELIHOOD THAT CLAIMS 1-10, 13-14 ARE OBVIOUS

Independent Claim 1 (and therefore dependent Claims 2-10, 13-14 as well) requires administration of an anti-CD20 antibody and CHOP in combination with stem cell transplantation to treat elderly patients with DLCL. Dependent claims add limitations requiring that the anti-CD20 antibody is rituximab, that the anti-CD20 antibody and CHOP are administered concurrently or both on Day 1, and that the dose of rituximab given is 375 mg/m^2 and six or eight chemotherapy cycles are given; among other limitations.

A. No Motivation To Administer An Anti-CD20 Antibody And CHOP Together During Transplantation (Claims 1-10, 13-14)

Petitioner fails to cite any art that discloses administering either an anti-CD20 antibody or CHOP during a stem cell transplantation regimen.

The only references cited by Petitioner that even mention transplantation are McNeil (Ex. 1006), Armitage (Ex. 1008), and Maloney (Ex. 1009). But Petitioner failed to identify any teaching in these references that an anti-CD20 antibody or CHOP, let alone the combination of rituximab and CHOP, should be administered during a transplantation regimen.

1. Petitioner Does Not Rely On McNeil

McNeil briefly mentions that "[o]ne more approach to NHL in the elderly involves peripheral stem cell transplants an approach that is combined with low-dose chemotherapy regimens," and that this approach was being tested. Ex. 1006 at 2. But McNeil nowhere suggests administering rituximab or CHOP during a transplantation regimen. *See* Ex. 2002 at 61:17-20. Petitioner does not allege otherwise.

2. Maloney Only Suggested Administering Rituximab After Transplantation

Maloney is an article reporting the results of a 20-patient clinical trial studying rituximab monotherapy in low-grade and intermediate/high-grade patients who have relapsed disease following first-line therapy with "chemotherapy," "bioimmunotherapy," "radiotherapy," or "ABMT [autologous bone marrow transplant]." *See* Ex. 1009 at 5, Table 2. Of the twenty patients, there were four "who had undergone prior high-dose therapy with ABMT" and reported results when rituximab monotherapy was used as second-line treatment for relapsed

disease. *Id.* at 8. The article does not indicate whether any of these four patients had DLCL. *Id.* at 5.

In the Discussion section of the article, the authors accordingly reported that these results indicated that rituximab could be used "***following***" transplantation regimen:

> Since this antibody does not appear to impair marrow reserves, it could possibly be used in patients who are myelosuppressed due to recent chemotherapy or following high dose chemotherapy with ABMT or peripheral stem-cell rescue.

Id. at 10. Petitioner relies on this statement to argue that Maloney taught that the combination of rituximab and CHOP should be given during a transplantation regimen. *See* Pet. 22. Not so.

The quoted sentence in Maloney suggests giving rituximab "following" a transplantation regimen because rituximab would not further exacerbate a patient's myelosuppression[10] from the high dose chemotherapy with ABMT or peripheral stem-cell rescue. *See* Ex. 1009 at 10. This teaching is based on the study's four patients "who had undergone prior high-dose therapy with ABMT" and reported responses with rituximab monotherapy as second-line treatment for relapsed

[10] Myelosuppression is a decrease in bone marrow activity, resulting in fewer red blood cells, white blood cells, and platelets. Ex. 2023.

disease. *Id.* at 8. The cited sentence in Maloney does not teach giving rituximab during a transplantation regimen.

In any event, Maloney does not teach giving rituximab with ***CHOP*** with a transplantation regimen. Maloney explained that rituximab could be used after transplantation because rituximab would not further exacerbate the patient's myelosuppression. But giving CHOP and rituximab would contradict this purpose, as CHOP would exacerbate the myelosuppression. *See* Ex. 2011 at 7 (reporting that "myelosuppression[, including reduced white blood cells and platelets,] appeared to be cumulative" in the CHOP treatment group); Ex. 1004 at 7 (reporting that "[r]easons for premature discontinuation of therapy in patients treated with CHOP included myelosuppression with sepsis").

In any event, a POSA would not have been motivated to administer all three therapies (CHOP, rituximab, and stem cell transplantation) to a patient because the art had not even shown that any combination of two of the three therapies (rituximab and CHOP, CHOP and a stem cell transplantation regimen, or rituximab and a stem cell transplantation regimen) was better than each therapy of the combination alone in DLCL patients >60 years old. Petitioner's proposed expert Dr. Ozer confirmed at deposition, "[i]f more testing was needed [] to determine whether [a] combination therapy was more effective and still safe, then a person of

ordinary skill in the art would test the combination therapy further before trying to add a third drug." Ex. 2002 at 27:12-18.

3. Armitage Does Not Mention Rituximab Or CHOP

Armitage is a textbook chapter that discusses stem cell transplantation generally, for a variety of different cancers. *See* Ex. 1008. There is no discussion of CHOP or rituximab anywhere in the reference, let alone how either or both could be used during a transplantation regimen. *Id.*

Citing Armitage and Maloney, Petitioner appears to argue that the combination of rituximab and CHOP would be used as "induction therapy" with a transplantation regimen. *See* Pet. 36. But neither Armitage nor Maloney even use the word "induction therapy," let alone suggest that such therapy should include rituximab and CHOP in an elderly patient with DLCL undergoing a transplantation regimen.

A POSA would have known that chemotherapy regimens given with stem cell transplantation regimens in lymphoma patients included BACT, TACC, BEAM, BAVM, CBV, ABV, melphalan, and BAC. *See* Ex. 2005 at 3. As discussed in Section II.A.2, CHOP was given as first-line treatment for DLCL patients. But because there was a lifetime limit on the amount of doxorubicin that could be given to a patient, CHOP was not used as salvage therapy for patients who relapsed after first-line CHOP treatment. *See* Section II.A.2. Transplantation

regimens were given as salvage therapies to relapsed patients who had responded to first-line chemotherapy. *See* Ex. 1013 at 12 (identifying transplantation regimens as salvage therapy); Ex. 2005 at 3 (administering transplantation regimens as salvage therapy).

As discussed in Section IV.A, the claimed invention requires that the anti-CD20 and CHOP be given during a transplantation regimen. The claims do not encompass patients who received rituximab only as part of first-line therapy with CHOP, subsequently relapsed, and then received a transplantation regimen that did not include rituximab and CHOP.

In sum, Petitioner has failed to cite any evidence indicating that rituximab or CHOP, let alone a combination of both, was given as induction therapy during a transplantation regimen.

B. No Motivation To Administer An Anti-CD20 Antibody And CHOP Concurrently Or Both On Day 1 During Transplantation (Claims 7, 9, 13-14)

For reasons discussed in Section V, a POSA would not have been motivated to administer rituximab and CHOP "concurrently" or both on "Day 1," as required by Claims 7 and 9, respectively. Petitioner's Ground II fails for these additional reasons as well.

C. No Reasonable Expectation Of Success Because Of Toxicity Concerns With Administering Rituximab And CHOP During Transplantation In Elderly Patients (Claims 1-10, 13-14)

Petitioner has also failed to show, as it must, that there was a reasonable expectation of success using rituximab and CHOP during a transplantation regimen in elderly patients.

As discussed in Section V.B, there was insufficient literature to support a reasonable expectation of success for giving rituximab and CHOP to elderly patients—even without the addition of a transplantation regimen. A POSA would have known that the toxicity risk would substantially increase if rituximab and CHOP were administered during a transplantation regimen, which Dr. Ozer acknowledged is a "potentially lethal" therapy even on its own. Ex. 2002 at 38:11-14. Indeed, Dr. James Armitage, the author of Petitioner's transplantation reference, Ex. 1008, warned in another publication that transplantation was especially risky for elderly patients, to the point that most elderly patients were not even eligible for autologous bone marrow transplantation (ABMT) regimens because of "an unacceptably high treatment-related death rate." Ex. 2003 at 6. In view of this, Dr. Armitage's later publication, relied on by Petitioner, which merely says that ABMT can be "applicable" to patients 60-70 years of age (Ex. 1008 at 6), does not support a reasonable expectation of success.

As discussed in Section VI.A, the only cited references that even mention transplantation are McNeil, Maloney, and Armitage. None of these provides a reasonable expectation for administering rituximab and CHOP during a transplantation regimen for elderly patients with DLCL. As discussed in Section VI.A, these references do not suggest the use of rituximab or CHOP ***during*** a transplantation regimen, let alone provide any clinical results that would support a reasonable expectation of success. The Armitage textbook chapter, in fact, devotes three pages to listing the lethal toxicities that can occur with a transplantation regimen. *See* Ex. 1008 at 6-8 (listing complications such as "profound immune suppression that accompanies GVHD [graft-versus-host disease]," lethal "pulmonary complications," liver disease, development of new diseases such as diabetes, and "rapidly progressive heart failure and death," among others).

D. No Reasonable Expectation Of Success For Administering Six Or Eight Chemotherapy Cycles In Elderly Patients (Claim 13)

For reasons discussed in Section V.C, there is no expectation of success for ***six or eight*** CHOP cycles in the claimed elderly patients, as required by Claim 13.

E. No Reasonable Expectation Of Success For Administering Eight Chemotherapy Cycles In Elderly Patients (Claim 14)

For reasons discussed in Section V.D, there is no expectation of success for ***eight*** CHOP cycles in the claimed elderly patients, as required by Claim 14.

VII. GROUND III — PETITIONER FAILS TO ESTABLISH A REASONABLE LIKELIHOOD THAT CLAIMS 11-12, 15-16 ARE OBVIOUS

The only difference between Ground I and Ground III is the removal of Coiffier (Ex. 1007). *See* Pet. 57. This Ground, therefore, fails for the same reasons Ground I fails.

Petitioner concedes, as it must, that Coiffier is the only reference that provides clinical data on the use of rituximab monotherapy. *See* Pet. 57-58.[11] Coiffier was also the only reference that disclosed administering rituximab for up to eight doses. Without this reference, there would have been even less of an expectation of success for the combination of rituximab and CHOP to treat elderly patients with DLCL, as required by Claims 11-12, 15-16. All the more so for Claim 16, which requires eight doses of rituximab with eight cycles of CHOP.

VIII. GROUND IV — PETITIONER FAILS TO ESTABLISH A REASONABLE LIKELIHOOD THAT CLAIMS 1-10, 13-14 ARE OBVIOUS

The only difference between Ground II and Ground IV is the removal of Coiffier (Ex. 1007). *See* Pet. 59. This Ground, therefore, fails for the same reasons Ground II fails.

[11] As discussed in Section V.B.5, Dr. Ozer conceded that Coiffier does not in fact disclose whether the elderly patients enrolled in the study responded to rituximab monotherapy. *See* Ex. 2002 at 55:10-15.

For reasons discussed in Section VII, without Coiffier, there would have been even less of an expectation of success for using rituximab, CHOP, and transplantation to treat elderly patients with DLCL. All the more so for Claim 14, which requires eight doses of rituximab with eight cycles of CHOP.

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 in part*, 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 '744 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).

X. CONCLUSION

For the reasons set forth above, Patent Owner respectfully submits that the Board should deny the Petition for *inter partes* review in its entirety.

Dated: March 19, 2018

Respectfully submitted,

/s/ Michael Fleming

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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 13,998 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: March 19, 2018

Respectfully submitted,

/s/ Pia Kamath
Pia Kamath

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. 42.6, the undersigned certifies that on March 19, 2018, a copy of **BIOGEN, INC.'S PATENT OWNER PRELIMINARY RESPONSE** and **EXHIBITS 2001-2024** were served by electronic mail upon the following:

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