UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,

Petitioner,

v.

BIOGEN, INC.
Patent Owner.

Case IPR2017-01168
U.S. Patent No. 8,821,873

PATENT OWNER RESPONSE

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I. INTRODUCTION

Diffuse large cell lymphoma ("DLCL") is an aggressive subtype of non-Hodgkin's lymphomas ("NHLs"). In the late 1990s, DLCL was particularly difficult to treat among elderly patients >60 years old. A combination chemotherapy called "CHOP" reportedly cured only about half as many elderly patients as younger patients, and was more toxic in elderly patients.

In U.S. Patent No. 8,821,873 ("the '873 patent"), Patent Owner Biogen, Inc. claims methods of treating DLCL patients >60 years old comprising administering an anti-CD20 antibody and CHOP, "wherein the anti-CD20 antibody is administered to the patient in combination with stem transplantation regimen." Petitioner Pfizer, Inc. sought *inter partes* review of the '873 patent, and the Board instituted trial on a single ground to determine whether the five-reference combination of Moreau (Ex. 1007), Link (Ex. 1005), McNeil (Ex. 1003), Maloney (Ex. 1008), and Coiffier (Ex. 1006) renders obvious claims 1-5 of the '873 patent.

The Board's decision to institute trial relied in part on the declaration of Petitioner's proposed expert, Dr. Howard Ozer, who opined that the claims of the '873 patent would have been obvious. *See, e.g.*, Paper 6, 10. But when cross examined at deposition on whether he read the '873 patent before submitting his declaration, Dr. Ozer testified: "No, I submitted my declaration then received the patent." Ex. 2008, 63:17-20. To avoid any doubt, counsel for Patent Owner then

asked Dr. Ozer: "So at the time you signed your declaration, you had not read the patent, is that correct?" *Id.* at 63:22-24. Dr. Ozer answered unequivocally: "Correct." *Id.* at 64:1. [1] The Board should weigh Dr. Ozer's declaration accordingly.

The Board should confirm all five claims. Petitioner's challenge fails for several reasons:

First, Petitioner did not identify any disclosure in the prior art of administering an anti-CD20 antibody in combination with a stem cell transplantation regimen to a patient of any age, let alone to a DLCL patient > 60 years old.

Second, Petitioner failed to establish a motivation to modify and combine the alleged prior art to arrive at the claimed invention. Petitioner argues that Moreau, which described a method involving administration of three doses of CHOP followed later by a stem cell transplantation regimen for patients who responded to the CHOP, "taught all but one element—the addition of rituximab—of claim 1." Pet. 44.

Petitioner tries to address this missing element by taking the position that a POSA would have been motivated to add rituximab to the those three doses of

[1] Petitioner tried to get Dr. Ozer to change this testimony on re-direct with leading questions.

CHOP to produce a treatment that included administering CHOP, rituximab, and a stem cell transplantation regimen to a patient. But a POSA would not have been motivated to administer all three therapies 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—especially 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. 2008, 27:12-18.

Moreover, adding rituximab to the three doses of CHOP chemotherapy in Moreau would have made it impossible for a POSA to discern whether patients were responsive to the chemotherapy—a prerequisite to proceeding on to the stem cell transplantation regimen. A patient responding to treatment with both rituximab and CHOP might simply be responsive to rituximab, but refractory to chemotherapy. Accordingly, a POSA would not have been inclined to add rituximab to the three doses of CHOP in Moreau.

Contrary to Petitioner's suggestion, none of Link, McNeil, or Maloney would have motivated a POSA to add rituximab to the three doses of CHOP in

Moreau. These references report studies of various therapies, but do not identify any responders as DLCL patients >60 years old, as claimed.

Petitioner also failed to establish that adding rituximab to the three doses of CHOP in Moreau would have resulted in the invention of the claims, as properly construed. According to the intrinsic evidence, administering an anti-CD20 antibody in combination with a stem cell transplantation regimen means administering the antibody *during* a stem cell transplantation regimen. Petitioner never contended that adding rituximab to the three doses of CHOP in Moreau would have resulted in administering rituximab during a stem cell transplantation regimen.

Third, Petitioner failed to establish that a POSA would have had a reasonable expectation of success. Indeed, the petition lacks any meaningful analysis of the "reasonable expectation of success" requirement. It mentions reasonable expectation of success only a handful of times, including as a couple of naked conclusions. Otherwise, it argues that there would have been a reasonable expectation of success because Link allegedly "teaches that the toxicity of rituximab does not overlap with the toxicity of CHOP therapy." But that is a non-sequitur. The absence of overlapping toxicity is not the measure of a successful treatment.

Dr. Ozer's declaration in support of the petition contains even less discussion of a reasonable expectation of success than the petition does. It simply acknowledges that the law requires a reasonable expectation of success and then parrots the requirement as a throwaway conclusion at the end of a paragraph addressing a different requirement (motivation to combine).

Fourth, Petitioner failed to establish that adding rituximab to the three doses of CHOP in Moreau would have been obvious to try. Petitioner fails to establish that the claimed invention was one of a finite number of identified solutions. Instead, Petitioner artificially focuses on elements of the claims and argues that those elements constitute the entire universe of available options to treat patients. Petitioner's own references, and its own proposed expert, disprove this. In any event, an obvious-to-try analysis focuses on an invention as a whole.

Petitioner not only failed to show that the claimed invention was one of a finite number of identified solutions, but also failed to show that any such solutions were predictable. It is well-established that medicinal treatment is one of the unpredictable arts.

For all these reasons, and the further reasons articulated below, Petitioner's challenge fails and the Board should confirm claims 1-5 of the '873 patent.

II. TECHNICAL BACKGROUND AS OF THE PRIORITY DATE

Lymphomas are cancers involving uncontrolled growth of B cells or T cells. Ex. 1013, 3; Ex. 2011, ¶ 27. There are multiple kinds of lymphomas. Ex. 2011, ¶ 28; Ex. 1002, ¶ 33. As Dr. Ozer states, "[e]ach lymphoma has its own distinct genetic**,** immunologic**,** and molecular characteristics." Ex. 1002, ¶ 33; Ex. 2011, ¶ 28.

As of August 1999, a POSA would have known that determining what kind of lymphoma a patient had was important because it impacted the patient's treatment and treatment outcomes. Ex. 2011, ¶¶ 20, 26, 28; Ex. 1002, ¶ 33; *id.* at ¶ 37 (noting that "the same types of chemotherapeutic agents were not used for all types of NHL"); Ex. 2008, 16:12-17:1.

Physicians classified the various lymphomas themselves into three categories: low, intermediate, or high grade. Ex. 1011, 1. Each grade comprised multiple different types of lymphomas. *Id.* at 2 (Table 1); Ex. 2011, ¶ 29.

Physicians further classified lymphoma patients according to the stages of their diseases. The most commonly used staging system for NHL was the Ann Arbor Staging System, which comprises four stages I-IV. Ex. 1010, 3 (Table III); Ex. 2011, ¶ 30. Higher stages were associated with poorer survival. Ex. 1013, 4. Stages III and IV were considered "advanced-stage" disease. Ex. 2011, ¶ 30.

A. Diffuse Large Cell Lymphoma

Diffuse large cell lymphoma ("DLCL") was known to be a subtype of non-Hodgkin's lymphomas ("NHLs"), which are cancers caused by the malignant growth of B lymphocytes. *See* Ex. 1001, 1:25-26; Ex. 2011, ¶¶ 31, 32.

DLCLs are intermediate- or high-grade lymphomas, identified as "Type G" by the International Working Formulation ("IWF") classification. Ex. 1010, 2. Under the Revised European American Lymphoma ("REAL") classification, DLCLs are a type of "aggressive" NHL. *Id.*; Ex. 2011, ¶ 33.

B. Treatments Of Diffuse Large Cell Lymphoma

1. Front-Line Chemotherapy

Upon diagnosing a patient with DLCL, physicians would strive to drive the disease into remission with treatment. Ex. 2011, ¶ 34. Physicians sometimes referred to "remission" as "complete remission," which meant a patient was free of detectable disease, in contrast to "partial remission," which meant that disease was still detectable in the patient. *Id.* Physicians did not set out to achieve only partial remissions, which will not lead to cure. *Id.*

Another phrase used to describe a "complete remission" was "complete response." *Id.* at ¶ 35. And another phrase used to describe a "partial remission" was "partial response." *Id.*

The first treatment administered to the patient was called "front line" or "up front" treatment, or "primary therapy." *Id.* at ¶ 36. This could be one treatment or a course of treatments. *Id.* A single "line" or "course" of treatment referred to one or more therapies administered together or in succession without the patient relapsing in between. *Id.* Typically, "front line" or "up front" treatment for DLCL as of August 1999 consisted of administering one or more chemotherapy drugs. *Id.* Several different chemotherapies were available at the time, including m-BACOD, ProMACe-CytaBOM, and MACOP-B regimens. Ex. 1013, 11 (Table 111-8).

Another chemotherapeutic regimen available at the time was called "CHOP," which stood for: cyclophosphamide (C), hydroxydaunorubicin (H),[2] Oncovin (O),[3] and prednisone/prednisolone (P). Ex. 1010, 1; Ex. 1001, 8:40-43; Ex. 2011, ¶ 37. CHOP regimens were usually administered to patients over 21-day cycles. Ex. 2011, ¶ 38. The standard CHOP regimen used for inducing remission in DLCL patients was 6 to 8 cycles of CHOP. Ex. 1002, ¶¶ 40, 42; Ex. 2008, 28:23-25, 28:14-17; Ex. 2011, ¶ 38. A POSA would have known that the CHOP regimens aimed at achieving induction of remission in patients with Stage III or IV

[2] Hydroxydaunorubicin was also called "doxorubicin." Ex. 2011, ¶ 39 n.1.

[3] Oncovin was a brand name for the drug "vincristine." Ex. 2011, ¶ 39 n.2.

(advanced-stage) disease typically used eight cycles of CHOP. Ex. 1013, 11; Ex. 2011, ¶ 38.

These CHOP regimens produced complete responses in 50-60%, Ex. 2008, 28:18-22, or more, of DLCL patients. Ex. 2011, ¶ 39. But not all of those patients experienced long-term remission or cure. Many patients would relapse.

2. Stem Cell Transplantation Regimens For Relapsed Patients

One strategy for treating relapsed intermediate- and high-grade lymphoma patients was to administer very high amounts of a chemotherapy such as "BEAM"[4] in an attempt to destroy more cancer cells, including those that were not destroyed by the front-line treatment. Ex. 2011, ¶ 40; Ex. 1002, ¶ 43. Because such high amounts of chemotherapy wiped out the patient's bone marrow, physicians would then infuse stem cells into the patient to help restore the patient's immune system. Ex. 2011, ¶ 40.

The stem cells could be harvested directly from bone marrow, as part of a "bone marrow transplantation" (BMT) regimen, or from circulating blood, as part of a "peripheral blood stem cell transplantation" (PBSCT) regimen. Ex. 2011, ¶ 41.

"Allogenic" stem cell transplantation regimens used stem cells from another person "whose bone marrow matche[d]" the patient's, while "autologous stem cell

[4] The acronym BEAM stands for BiCNU (B), etoposide (E), Ara-C (A), and melphalan (M).

transplantation" (ASCT) regimens used a patient's own stem cells. Ex. 2003, 1; Ex. 2011, ¶ 42.

Autologous stem cell transplantation regimens thus involved at least the following steps: (1) harvesting the patient's stem cells, (2) treating the patient with high doses of chemotherapy in what was called a "conditioning" step, and (3) infusing the stem cells back into the patient's blood. Ex. 2003, 2-3; Ex. 2011, ¶ 43.

When the stem cells were harvested from the bone marrow, an ASCT regimen could include an "in vivo purging" stage to reduce the number of cancer cells in the marrow to be extracted. Ex. 2008, 37:19-23. When the stem cells were harvested from the peripheral blood, the ASCT regimen sometimes included a "mobilization" stage to push stem cells out of bone marrow and into circulation to be harvested. Ex. 2011, ¶ 44; Ex. 2008, 37:24-38:3.

As Dr. Ozer confirmed at his deposition, a POSA would have understood that it was important for stem cell transplantation patients to have chemotherapy-sensitive, also referred to as "chemosensitive," disease. Ex. 2008, 38:23-39:1. This was because the patient was going to be administered a high dose chemotherapy at the conditioning stage of the stem cell transplantation regimen. *Id.* at 39:2-6. The high-dose chemotherapy administered during the "conditioning" stage carried with it potentially serious toxicities and side effects. *Id.* at 39:12-17. Indeed, stem cell

transplantation regimens were potentially lethal. Ex. 2011, ¶ 45. If a patient's disease was not chemosensitive—but rather was refractory to chemotherapy—then a physician would potentially be putting the patient through the stem cell transplantation regimen unnecessarily. This, of course, was something physicians did not want to do. Ex. 2008, 39:7-25; Ex. 2011, ¶ 45.

Studies showed that a patient whose disease was refractory to chemotherapy was not a good candidate to begin a stem cell transplantation regimen. Ex. 2011, ¶ 46. For example, the results of a study investigating the role of high-dose combination chemotherapy and autologous bone marrow transplantation (ABMT) in the management of patients with NHL who had failed conventional therapy reported that for patients "who still had chemotherapy-responsive disease, the procedure had low toxicity and a high response rate," whereas patients "who have no response to chemotherapy" had little further response to the conditioning treatment, which "may also be associated with high and perhaps unacceptable levels of morbidity and procedure-related mortality." Ex. 2004, 7-8. Another study confirmed that there was a significant difference in the efficacy of high-dose therapy and ABMT between patients that were sensitive to chemotherapy and patients that were not. Ex. 2005, 5. These results "were largely confirmed by the results reported by other single-institution trials and by the European Bone Marrow

Transplantation Registry," which suggested using "an early ABMT procedure . . . in patients with 'chemosensitive' disease." Ex. 1010, 12.

Based on these results, guidelines for the treatment of aggressive NHL from 1997 stated that for "patients whose disease is resistant to salvage chemotherapy at the time of relapse[,] . . . there is a poor outcome which probably does not justify the use of ABMT." *Id.*; Ex. 2011, ¶ 47.

Accordingly, physicians would try to make sure that a patient's disease was chemosensitive before starting the patient on a stem cell transplantation regimen. Ex. 2008, 39:21-25; Ex. 2011, ¶ 48. Physicians would do this by administering chemotherapy to the patient before such a regimen. Ex. 2011, ¶ 48. As Dr. Ozer confirmed at deposition, as of the priority date, "it was known that a patient whose disease is refractory to chemotherapy is not a good candidate to begin a stem cell transplantation regimen." Ex. 2008, 39:7-11; Ex. 2011, ¶ 48.

C. Treatment of NHL Patients >60 Years Old

As of the priority date, a POSA would have known that age was a critical prognostic factor for NHL. 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 intermediate- and high-grade lymphoma." Ex. 1003, 1; Ex. 2008, 20:12-18; Ex. 2011, ¶ 49.

"The pharmacokinetic processes of absorption, distribution, metabolism and elimination of drugs and their metabolites from the body [were known to be] significantly different in the elderly, due mainly to alterations in body composition and organ function." Ex. 2007, 4. Further, it was known that "the target action of a drug may be affected by age related changes in physiologic homeostatic mechanisms such as postural control, orthostatic circulatory responses, thermo regulation, visceral muscle function and higher cognitive function." *Id.* Moreover, it was accepted that there was "exaggerated drug toxicity" among elderly patients. *Id.*; Ex. 2011, ¶ 50.

A POSA would have known that "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." Ex. 1002, ¶ 52; Ex. 2011, ¶ 51. CHOP was known to cause more adverse events in patients greater than 60 years old. Ex. 2008, 31:6-8; *see also* Ex. 1003 at 1 (stating that CHOP "is more toxic in [the elderly] age group"). And CHOP reportedly cured "only about half as many elderly patients as younger patients." Ex. 1003, 1; Ex. 2008, 41:25-42:2.

Moreover, autologous stem cell transplantation (ASCT) was usually not an option for elderly patients. Rather, ASCT was "usually restricted to patients aged ≤ 60 years, partly due to the anticipated poor tolerance of intensive treatment in elderly patients." Ex. 1007, 1; Ex. 2011, ¶ 52.

Dr. Ozer asserted in his declaration that "CHOP chemotherapy followed by PBSCT was standard-of-care treatment for all DLCL patients, including elderly patients." Ex. 1002, ¶ 87. But Dr. Ozer was unable to defend that assertion at deposition. When asked for the basis of the assertion, Dr. Ozer pointed to a sentence in Moreau that contains no mention of DLCL or elderly patients, and refers only to patients "who relapse after primary therapy." Ex. 2008, 64:11-20; Ex. 1007, 1. Moreover, Dr. Ozer conceded that the very next sentence of Moreau says of ASCT that instead of being standard of care for elderly patients, "it's usually restricted to patients less than or equal to 60." Ex. 2008, 66:23-67:10; *see also* Ex. 2011, ¶ 53.

III. U.S. PATENT NO. 8,821,873

U.S. Patent No. 8,821,873 traces its priority back to a provisional application filed on August 11, 1999. Ex. 1001, 1:8-11. Petitioner adopts that date as the priority date for purposes of the petition. Pet. 9.

A. Claims

All claims in the '873 are directed to a method of treating a patient >60 years old with DLCL. Ex. 1001, 8:36-56; Ex. 2011, ¶¶ 14-19.

Independent claim 1 is "[a] method of treating a patient with diffuse large cell lymphoma comprising administering anti-CD20 antibody and chemotherapy to the patient, wherein the patient is >60 years old, wherein the chemotherapy

comprises CHOP (cyclophosphamide, hydroxydaunorubicin/doxorubicin, vincristine, and prednisone/prednisolone), and wherein the anti-CD20 antibody is administered to the patient in combination with stem cell transplantation regimen." Ex. 1001, 8:37-44. Similarly, independent claim 5 is directed to administering rituximab and CHOP to a >60 year old patient, in combination with stem cell transplantation. *Id.* at 8:51-56.

Dependent claim 4 recites the method of claim 1, "wherein the lymphoma is accompanied by bone marrow involvement." *Id.* at 8:49-50.

B. Person Having Ordinary Skill In the Art

As of the August 11, 1999 priority date, a person having ordinary skill in the art ("POSA") would have on average been be a practicing oncologist with at least an M.D. degree and about one to three years of experience treating patients with NHL. "[T]hat's my definition" of a POSA, Dr. Ozer confirmed at deposition. Ex. 2008, 15:11-15; Ex. 2011, ¶¶ 21-23.

In his declaration, Dr. Ozer wrote that, alternatively, a POSA might have experience "researching treatments for NHL, including therapeutic drugs." Ex. 1002, ¶ 15. But that alternative does not describe a person whose skill in the art was only ordinary. Ex. 2011, ¶ 24. It describes a person whose skill in the art was extraordinary. *Id.* As Dr. Kahl explains, "[o]nly a tiny fraction of oncologists in 1999 had (or even have now) experience researching treatments for NHL, and

those oncologists were innovators," not people having only ordinary skill in the art. *Id.*

The "Field of the Invention" section of the patent states that "[t]he present invention concerns methods of treating intermediate- and high-grade non-Hodgkin's lymphomas." Ex. 1001 at 1:17-18. Dr. Kahl points out that "[o]ncologists having ordinary skill in that field would have had experience treating patients, but would not have had experience researching new treatments for patients." Ex. 2011, ¶ 25.

IV. CLAIM CONSTRUCTION

A POSA would have understood the phrase "the anti-CD20 antibody is administered to the patient in combination with stem cell transplantation regimen" to mean that "the anti-CD20 antibody is administered to the patient during a stem cell transplantation regimen." *Id.* at ¶¶ 54-55.

A. According To The Plain Language Of The Claims, The Anti-CD20 Antibody Is Required To Be Administered In Combination With Stem Cell Transplantation

"[T]he claims themselves provide substantial guidance as to the meaning of particular claim terms." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (en banc). "[T]he context in which a term is used in the asserted claim can be highly instructive." *Id.*

Independent claim 1 describes a method of treating a patient with DLCL by administering "anti-CD20 antibody and chemotherapy" and specifies that the "anti-CD20 antibody is administered to the patient in combination with stem cell transplantation regimen." Ex. 1001, 8:37-44. Independent claim 5 describes a similar method, but with rituximab as the anti-CD20 antibody. A POSA would have understood this to mean that the anti-CD20 antibody must be administered to the patient during a stem cell transplantation regimen. Ex. 2011, ¶ 56 .

B. 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 Inc.*, 844 F.3d 945, 948 (Fed. Cir. 2016) (internal citations and quotation marks omitted).

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.[5]" Ex. 1001, 6:13-17 (emphasis added). A POSA would have understood this to be teaching that the anti-CD20

[5] The '873 patent describes each of the terms in this list. Ex. 1001, 6:17-53. For example, the patent states that "'[i]nduction' is meant to refer to the initial therapies aimed at achieving induction of remission." *Id.* at 6:17-20.

antibody is administered at any time during bone marrow or stem cell transplantation, including at the listed times—or any other time—during a stem cell transplantation regimen. Ex. 2011, ¶ 57.

"The present invention," the specification states, "includes administering anti-CD20 antibodies, or other lymphoma depleting antibodies, ***as part of a transplant regimen*** (autologous bone marrow transplant or allogeneic bone marrow transplant or peripheral blood stem cell transplant) to improve the survival of transplant recipients." Ex. 1001, 2:34-39 (emphasis added). As Dr. Ozer confirmed at deposition, "[a] person having ordinary skill in the art would have understood that administering anti-CD20 antibodies as part of a transplant regimen means administering the antibodies during the transplant regimen"—"[a]t any point in the transplant." Ex. 2008, 66:8-12; Ex. 2011, ¶ 58.

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 with less concern about reintroducing tumor cells originally harvested with the marrow back into the patient." Ex. 1001, 6:54-58 (emphasis added). A POSA would have understood that rituximab treatment "at the various stages of transplantation" refers to rituximab treatment during the transplantation regimen. Ex. 2011, ¶ 59.

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 the "conditioning" stage after stem cell harvesting. Ex. 2008, 38:4-7. Other stages include in vivo purging and mobilization. *Id.* at 37:19-38:3. Even administration of an anti-CD20 antibody at an induction stage of a stem cell transplantation regimen can fall within the scope of the claims.

C. Petitioner's Proposed Construction Is Inconsistent With The Intrinsic Evidence.

In his declaration, Dr. Ozer contends that "the term 'the antibody [sic] CD20 antibody is administered to the patient in combination with stem cell transplantation regimen' in the context of claim 1 includes the administration of the anti-CD20 antibody (e.g., rituximab) before the stem cell transplantation, as well as 'rituximab treatment at the various stages of transplantation' and even 'subsequent to' such transplant." Ex. 1002, ¶ 28. But the claims require that an anti-CD20 antibody be administered during (*e.g*, "at the various stages of") the stem cell transplantation regimen, as discussed above. *See* Ex. 2011, ¶ 60.

Dr. Ozer asserts that "definitions" of procedures such as "in vivo purging" and "mobilization" in the specification confirm his position that administering the anti-CD20 antibody only before a stem cell transplantation regimen would be encompassed by the claims. *Id.* at ¶¶ 25-28. But the specification describes

administering rituximab in connection with such procedures when they take place "during bone marrow or stem cell transplant"—i.e., when they are stages of a stem cell transplantation regimen, as each may be. Ex. 1001, 6:13-17; Ex. 2011, ¶ 61. As Dr. Ozer confirmed at deposition, for example, "before harvesting, a stem cell transplantation regimen could include an in vivo purging stage geared towards purging tumor cells from the bone marrow." Ex. 2008, 37:19-23. "Alternatively, a stem cell transplantation regimen could include a mobilization stage by which stem cells are mobilized to leave the bone marrow and enter the circulatory system for harvesting." *Id.* at 37:24-38:3. Nowhere does the specification describe the invention as administering rituximab only before a stem cell transplantation regimen. Ex. 2011, ¶ 61.

Nor does the specification describe administering rituximab only after a stem cell transplantation regimen. Ex. 2011, ¶ 62. The specification states that after "rituximab treatment at the various stages of transplantation," a patient "may then benefit by additional or subsequent treatment with chimeric anti-CD20 antibody as part of a maintenance regimen, or by administration of a radiolabeled antibody such as Y2B8 to further decrease the chance of relapse." Ex. 1001, 6:54-63. But that describes administration of rituximab to a patient both during ***and*** after the stem cell transplantation regimen. Ex. 2011, ¶ 62. This is consistent with Patent Owner's construction because rituximab is still being administered during the stem

cell transplantation regimen (in addition to being administered to the same patient later). *Id.* So long as the anti-CD20 antibody is administered to a patient during a stem cell transplantation regimen, the claims do not exclude also administering an anti-CD20 antibody to the patient before and/or after that stem cell transplantation regimen.

V. PETITIONER FAILS TO ESTABLISH THAT ANY CLAIM OF THE '873 PATENT WOULD HAVE BEEN OBVIOUS

"Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination." *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). "Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention." *Id.* Moreover, "[a]n obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art." *Amgen Inc. v. F. Hoffman-La Roche, Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009).

"Importantly, the great challenge of the obviousness judgment is proceeding without any hint of hindsight." *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1375 (Fed. Cir. 2011). 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., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013).

None of the prior art discloses the claim element requiring "the anti-CD20 antibody [to be] administered to the patient in combination with stem cell transplantation regimen." Further, a POSA would not have had a reason or motivation to combine Moreau, Link, McNeil, Maloney, and Coiffier to administer an anti-CD20 antibody and CHOP to a DLCL patient > 60 years old, wherein the anti-CD20 antibody is administered during a stem cell transplantation regimen. *See* Ex. 2011, ¶¶ 63-70.

But even assuming otherwise, Petitioner's challenge fails because Petitioner never established the required reasonable expectation of success. *See Institut Pasteur v. Focarino*, 738 F.3d 1337, 1344 (Fed. Cir. 2013) (reversing a finding of obviousness because "one of ordinary skill in the art would not have reasonably predicted the successful adaptation of [the prior art] to target chromosomal DNA in eukaryotic cells," as claimed); *The Broad Inst. v. Regents of the Univ. of Cal.*, Patent Interference No. 106,048, 2017 Pat. App. LEXIS 1261, at *65 (P.T.A.B. Feb. 15, 2017) (finding that even though the prior art provided "a motivation" to combine, there was still insufficient evidence "indicat[ing that] ordinarily skilled artisans would have had any expectation of success" for practicing the invention).

The Board instituted trial in this proceeding based in part on Dr. Ozer's declaration, in which he opined that the claims of the '873 patent would have been obvious. *See, e.g.,* Paper 6, 10. But when counsel for Patent Owner cross examined Dr. Ozer at deposition on whether he read the '873 patent before submitting his declaration, Dr. Ozer testified: "No, I submitted my declaration then received the patent." Ex. 2008, 63:17-20. To make sure the record was clear, counsel for Patent Owner then asked Dr. Ozer: "So at the time you signed your declaration, you had not read the patent, is that correct?" *Id.* at 63:22-24. Dr. Ozer answered unequivocally: "Correct." *Id.* at 64:1.[6] The Board should weigh Dr. Ozer's declaration accordingly.

A. Petitioner Did Not Identify Any Disclosure In The Prior Art Of Administering An Anti-CD20 Antibody To A Patient In Combination With A Stem Cell Transplantation Regimen.

Independent claim 1 requires that "the anti-CD20 antibody is administered to the patient in combination with stem cell transplantation regimen." Ex. 1001, 8:37-44. Independent claim 5 contains a similar requirement, but with rituximab as the anti-CD20 antibody. But none of the prior art references discloses administering an anti-CD20 antibody in combination with a stem cell transplantation regimen to any patient of any age, let alone to a DLCL patient >60

[6] On re-direct, Petitioner used leading questions to try to get Dr. Ozer to change this testimony. Ex. 2008, 68:16-70:8.

years old.

As discussed in the "Claim Construction" section above, a POSA would have understood that the claims require administration of the anti-CD20 antibody during the stem cell transplantation regimen.

Petitioner asserts that Maloney taught using rituximab "'following high-dose chemotherapy with ABMT [autologous bone marrow transplantation] or peripheral stem-cell rescue'" and reported responses to rituximab monotherapy "'in patients heavily pretreated with chemotherapy, including aggressive regimens and ABMT.'" Pet. 22. But at most, that describes administration of an anti-CD20 antibody in relapsed patients after—not during—a stem cell transplantation regimen. Ex. 2011, ¶ 113. Moreover, that stem cell transplantation regimen was given as prior therapy. *Id.* And all of the patients in the Maloney study had relapsed since their prior therapies, e.g., ABMT, so Maloney was not describing a single course of treatment involving administration of both a stem cell transplantation regimen and an anti-CD20 antibody. Ex. 1008, 4 ("Adults with histologically confirmed, relapsed B-cell lymphoma that expressed the CD20 antigen were eligible."); Ex. 2011, ¶ 113.

Petitioner failed to identify any disclosure in the alleged prior art of administering an anti-CD20 antibody to a patient during a stem cell transplantation regimen. Ex. 2011, ¶¶ 104-109.

B. Petitioner Failed To Establish A Reason Or Motivation To Modify And Combine The References Of The Ground To Arrive At The Claimed Invention.

Petitioner's foundational reference is Moreau. Ex. 1007. Moreau reports a small, open-label study "to answer the question about the feasibility of PBSCT as front-line treatment up to the age of 65" in patients with aggressive, stage III-IV NHL. Ex. 1007, 1; Ex. 2011, ¶¶ 71, 75.

The method disclosed in Moreau started with "three consecutive courses of CHOP therapy" to determine which patients were eligible to begin a subsequent stem cell transplantation regimen.[7] Ex. 1007, 1; Ex. 2011, ¶ 73. Only those patients achieving either a partial response (PR) or a complete response (CR) after those

[7] In response to a question at deposition about these three doses of CHOP, Dr. Ozer volunteered that the investigators in Moreau "gave a fourth CHOP" cycle after stem cells were harvested. Ex. 2008, 46:6-11. Dr. Ozer's declaration in support of the petition focuses on the three doses of CHOP and makes no mention of a fourth dose of CHOP. Ex. 1002, ¶ 62 ("The patients received three courses of CHOP chemotherapy, CHOP being 'considered the standard first-line treatment in high-grade NHL.'"); *id.* at ¶ 87 ("Moreau taught that CHOP followed by transplantation of the peripheral blood . . . ."). Nor did the petition mention a fourth dose of CHOP. Because Petitioner did not make arguments based on a fourth dose of CHOP in Moreau, Patent Owners do not have any such arguments to respond to.

three doses of CHOP were eligible for PBSCT. Ex. 1007, 1; Ex. 2011, ¶¶ 73-74. Patients with refractory or progressive disease did not begin the stem cell transplantation regimen. Ex. 1007, 1; Ex. 2011, ¶ 73. Indeed, Moreau reports that they did "not proceed to PBSCT." Ex. 1007, 4; Ex. 2011, ¶¶ 73-74.

Petitioner argues that Moreau "taught all but one element—the addition of rituximab—of claim 1." Pet. 44. Petitioner attempts to address this missing element by contending that a POSA would have been motivated to add rituximab to the three doses of CHOP in Moreau. The Board should reject Petitioner's argument.

Even if Petitioner had shown that there existed a motivation to add rituximab to the three doses of CHOP in Moreau, Petitioner never even attempted to show that such an addition would have led to the invention of the claims, as properly construed. The claims of the '873 patent should therefore be confirmed for this additional reason as well.

1. A POSA Would Not Have Been Motivated To Add Rituximab To The Three Doses Of CHOP In Moreau.

Petitioner argues that a POSA would have been motivated to add rituximab to the three doses of CHOP in Moreau to produce a front-line treatment of administering CHOP, rituximab, and a stem cell transplantation regimen. But a POSA would not have been motivated to administer CHOP chemotherapy, an anti-CD20 antibody, and a stem cell transplantation regimen to the same patient in a

single course of treatment. And a POSA would not have been inclined to add rituximab to the three doses of CHOP in Moreau because it would have confounded the analysis of chemosensitivity.

Petitioner asserts that each of Link, McNeil, and Maloney would have motivated a POSA to add rituximab to the three doses of CHOP in Moreau, but that assertion does not withstand scrutiny.

It was Petitioner's burden to establish a reason or motivation to modify and combine the prior art to arrive at the claimed invention, *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1377 (Fed. Cir. 2016) (holding that it was Petitioner's burden to provide evidence that "a skilled artisan would have been motivated to combine the prior art references"), and Petitioner failed to carry that burden. Accordingly, the claims of the '873 patent should be confirmed.

(a) A POSA Would Not Have Been Motivated To Administer CHOP, An Anti-CD20 Antibody, And A Stem Cell Transplantation Regimen In A Single Course Of Treatment.

Petitioner contends that a POSA would have been motivated to add rituximab to the three doses of CHOP in Moreau to produce a front-line treatment of administering CHOP, rituximab, and a stem cell transplantation regimen. But as of the priority date in August 1999, no two of those therapies had been shown to be better than the individual therapies alone—even in lymphoma patients generally, let alone in the claimed DLCL patients >60 years old. Ex. 2011, ¶¶ 115-16.

Moreau did not demonstrate that CHOP chemotherapy followed by PBSCT was better than CHOP alone and PBSCT alone. *Id.* at ¶¶ 117, 79. Rather, Moreau simply concluded that "PBSCT can probably be performed in patients between 61 and 65 years of age." *Id.* at ¶¶ 77, 76.

Nor did Link demonstrate that CHOP chemotherapy plus anti-CD20 antibody therapy was better than CHOP alone and anti-CD20 antibody therapy alone. Ex. 2011, ¶ 117, 86. Link does not even report results for DLCL patients >60 years old as a group, let alone compare the results for that group to the results historically achieved in such patients using CHOP alone. Ex. 2011, ¶¶ 83, 128. Link also did not test using fewer than six doses of CHOP, either alone or with an anti-CD20 antibody.

None of the alleged prior art even tested an anti-CD20 antibody in combination with a stem cell transplantation regimen, let alone concluded that such a combination was better than each therapy individually. *Id.* at ¶ 117.

In short, more testing was needed to determine whether administering any two of CHOP chemotherapy, an anti-CD20 antibody, and a stem cell transplantation regimen together was more effective (and still safe) as compared to each therapy alone. *Id.* at ¶ 118.

The experts on both sides agree that if more testing was needed to determine whether a two-regimen combination therapy was more effective and still safe, then

a person of ordinary skill in the art would test the two-regimen combination therapy further before trying to add a third drug. *Id.* at ¶ 119. Indeed, Dr. Ozer confirmed at deposition that "if more testing was needed though to determine whether the 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. 2008, 27:12-18.

Accordingly, a person having ordinary skill in the art would not even have been motivated to administer CHOP chemotherapy, an anti-CD20 antibody, and a stem cell transplantation regimen in a single course of treatment to a DLCL patient > 60 years old. Ex. 2011, ¶ 120.

(b) Adding Rituximab To The Three Doses Of CHOP In Moreau Would Have Confounded The Analysis Of Patient Chemosensitivity.

A person having ordinary skill in the art would have understood that it was important for stem cell transplantation patients to have chemosensitive disease, as explained above. Ex. 2011, ¶¶ 45-48, 121. As Dr. Ozer confirmed at deposition, "it was known that a patient whose disease is refractory to chemotherapy is not a good candidate to begin a stem cell transplantation regimen." Ex. 2008, 39:7-11.

Indeed, a person having ordinary skill in the art would have known that stem cell transplantation was not indicated for patients who did not have chemosensitive disease. Ex. 1010, 12 (explaining that for "patients whose disease is resistant to

salvage chemotherapy at the time of relapse[,] . . . there is poor outcome which probably does not justify the use of ABMT"); Ex. 2006, 1 ("High-dose therapy with autologous hematopoietic stem-cell support has been proposed as a potentially curative treatment for patients with recurrent, aggressive non-Hodgkin's lymphoma that remains sensitive to further standard chemotherapy."); Ex. 2004, 8 (reporting that stem cell transplantation studies confirm "that those patients who have no response to chemotherapy at conventional doses have little further response to dose escalation that may also be associated with high and perhaps unacceptable levels of morbidity and procedure-related mortality"); Ex. 2011, ¶ 122.

Accordingly, physicians would administer chemotherapy to a patient shortly before starting the patient on a stem cell transplantation regimen. Ex. 2011, ¶ 123, 48.

Moreau administered three doses of CHOP to assess whether each patient was refractory to chemotherapy and not eligible to begin a stem cell transplantation regimen. Ex. 1007, 1; Ex. 2011, ¶¶ 124, 73. A POSA would have known that adding rituximab to those three doses of CHOP would have confounded that assessment. Ex. 2011, ¶ 124. The problem, as Dr. Kahl explains, is that a patient's response to such therapy would not necessarily indicate that the patient was sensitive to chemotherapy. *Id.* at ¶¶ 124, 6-10. Indeed, a responding patient might

be refractory to chemotherapy and might simply be responding to the rituximab. *Id.* If the patient received both rituximab and CHOP, then there would be no way to discern whether the patient was responding to the rituximab or to the CHOP, or both. *Id.* A person having ordinary skill in the art would therefore not have been inclined to add rituximab to the three doses of CHOP in Moreau. *Id.*

(c) None Of Link, McNeil, Or Maloney Would Have Motivated A POSA To Add Rituximab To The Three Doses Of CHOP In Moreau.

Petitioner fails to establish that any of Link, McNeil, or Maloney would have motivated a POSA to add rituximab to the three doses of CHOP in Moreau. Ex. 2011, ¶ 125.

(i) Link Would Not Have Motivated A POSA To Add Rituximab To The CHOP In Moreau.

Link is an abstract of a phase II, open-label pilot study of rituximab and CHOP in intermediate- and high-grade NHL patients, including patients with IWF type "D", "G," and "H" pathologies. Ex. 1005, 5; Ex. 2011, ¶ 80. Link treated thirty-one patients, thirty of whom were evaluable. Ex. 1005, 5; Ex. 2011, ¶ 81. All patients in Link "received six cycles of therapy" comprising "rituximab 375 mg/m^2 on day 1 of each 21 day cycle followed 48 hours later by CHOP." Ex. 1005, 5; Ex. 2011, ¶ 82, 129. Link contains no mention of stem cell transplantation. Ex. 1005, 5; Ex. 2011, ¶ 130. Link did not identify any patients in its study as >60 years old, and did not report results for DLCL patients as a group. Ex. 1005, 5;

Ex. 2011, ¶¶ 81, 126, 128. As Petitioner admits, "Link did not study patients over 60." Pet. 21.

The differences between Link and Moreau are significant. Whereas the patients in Moreau were >60 years old, Ex. 1007, 1, Petitioner concedes that "Link did not study patients over 60," let alone DLCL patients >60 years old. Pet. 21; *see also* Ex. 2011, ¶¶ 81, 126, 128; Ex. 1005, 5. At the time of invention, a POSA would have known that age was a critical prognostic factor for NHL. Ex. 2011, ¶¶ 49, 127. 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 intermediate- and high-grade lymphoma." Ex. 1003, 1; Ex. 2008, 20:12-18; Ex. 2011, ¶ 49. Dr. Ozer confirmed at deposition that "CHOP was known to cause more adverse events in patients greater than 60 years old." Ex. 2008, 31:6-8.

Petitioner argues that a POSA would have been motivated to add rituximab to three doses of CHOP in Moreau. But Link administered six doses of CHOP, not three. Ex. 1005, 5; Ex. 2011, ¶ 82, 129. Unlike Moreau, Link used a standard 6-8 cycles of CHOP. *See, supra,* 6-7; Ex. 2011, ¶ 38; Ex. 1002, ¶¶ 40, 42; Ex. 2008, 28:14-17. Link nowhere suggests using fewer than six doses of rituximab or CHOP in any patient. Ex. 1005, 5.

Moreover, Moreau administered the three doses of CHOP prior to a stem cell transplantation regimen (for those patients who responded), whereas Link did not combine its six doses of CHOP with a stem cell transplantation regimen.

Given that Link does not address the same type of patients described in Moreau (DLCL patients aged 61-65), the same number of CHOP cycles, or the same therapeutic setting (administration of CHOP prior to a possible stem cell transplantation regimen), a POSA would not have been motivated by Link to add rituximab to the three doses of CHOP given to Moreau's DLCL "patients aged >60-65 years" followed by a possible stem cell transplantation regimen. Ex. 1007 at 1; Ex. 2011, ¶ 130. Petitioner did not prove otherwise.

Citing ¶ 89 of Dr. Ozer's declaration, Petitioner argues that "Link would have motivated a POSA to combine rituximab to the regimen of CHOP and PBSCT disclosed in Moreau, because Link taught that CHOP in combination with rituximab is at least as effective as, but no more toxic than, CHOP alone." Pet. 44-45. But Dr. Ozer never opined that CHOP in combination with rituximab was shown by Link to be at least as effective as CHOP alone. Ex. 1002, ¶¶ 89, 86. Nor did he articulate any reason why a POSA supposedly would have added a third therapy to a two-regimen combination that was only "at least as effective" as one of the regimens alone. To the contrary, at deposition, he confirmed that a POSA would not have added a third drug to a combination before determining that the

combination was "more effective" than monotherapy. Ex. 2008, 27:12-18; Ex. 2011, ¶ 84. In any event, Link did not report results for any patients >60 years old, let alone DLCL patients > 60 years old. Ex. 2011, ¶¶ 81, 126, 131.

Citing Link itself, Petitioner argues that "Link further taught that adding rituximab to a regimen of CHOP is likely more effective than CHOP alone." Pet. 45. But the portion of Link upon which Petitioner relies—identified by Petitioner in a parenthetical—cannot bear the weight of Petitioner's assertion. *Id.* The portion of Link upon which Petitioner relies simply says: "This 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." Ex. 1005, 5 (emphasis added); Ex. 2011, ¶ 85. Stating that a therapy "may" offer higher response rates is far different from stating that a therapy "is likely" to offer higher response rates, or is even "at least as effective" as conventional CHOP therapy. Ex. 2011, ¶ 134.

In any event, Petitioner offers no reason for a POSA to have assumed that the results of Link would be applicable to DLCL patients > 60 years old—even at the full six doses, much less at half that number of doses to correspond to the three doses of CHOP in Moreau. Ex. 2011, ¶¶ 126-27, 131.

Even assuming that the results of Link would be applicable to DLCL patients > 60 years old at half the number of doses, a POSA still would not have

been motivated to add rituximab to the three doses of CHOP in the method of Moreau. Ex. 2011, ¶ 132. The POSA would have either believed or disbelieved that rituximab and CHOP "may offer higher response rates" than CHOP alone. If the POSA would have disbelieved that rituximab and CHOP "may offer higher response rates," then the POSA would not have been motivated to experiment further with rituximab and CHOP. *Id.* Conversely, if a POSA would have believed that rituximab and CHOP "may offer higher response rates," then the POSA would have been motivated to resolve that question before considering adding a stem cell transplantation regimen to the course of treatment. Ex. 2011, ¶¶ 119, 133. A POSA would have known that if administering rituximab and CHOP as front-line treatment yielded high enough response rates, the risks of also including potentially lethal stem cell transplantation as part of front-line treatment, might outweigh the potential benefits—particularly for patients >60 years old. *Id.*

Petitioner asserts that "it would have been obvious to a POSA to add rituximab to a reduced CHOP regimen to achieve the same efficacy as CHOP monotherapy but with less toxicity, or to add rituximab to the traditional number of CHOP cycles to achieve more efficacy without any added toxicity." Pet. 45. But Petitioner fails to establish that the alleged prior art would have provided a POSA with the requisite motivation to arrive at either of those endpoints for DLCL patients >60 years old, as discussed above and elsewhere herein. Moreover, a

POSA would not have added rituximab to the three doses of CHOP in Moreau in pursuit of either endpoint because Moreau also involved administering a stem cell transplantation regimen,[8] which adds significant toxicity. Petitioner does not even argue, much less offer evidence, that a POSA would have thought that rituximab, three doses of CHOP, and the highly toxic conditioning stage of a stem cell transplantation regimen would have "less toxicity" than CHOP monotherapy. Nor does Petitioner contend that a POSA would have thought it possible to administer rituximab, the traditional number of CHOP cycles, and the conditioning step of a stem cell transplantation regimen "without any added toxicity" relative to the traditional number of CHOP cycles alone (i.e., CHOP monotherapy).

(ii) ***McNeil Would Not Have Motivated A POSA To Add Rituximab To The CHOP In Moreau.***

McNeil is a news article entitled "Non-Hodgkin's Lymphoma Trials In Elderly Look Beyond CHOP." Ex. 1003, 1; Ex. 2011, ¶ 87. Although McNeil refers to intermediate-grade lymphoma, it nowhere mentions treating DLCL patients.

McNeil acknowledges "the new monoclonal antibody, IDEC-C2B8 (Rituxan®)" at the beginning of the article, Ex. 1003, 1, and another "approach to

[8] As discussed above, the stem cell transplantation regimen was administered only to patients who were not refractory to chemotherapy.

NHL in the elderly involv[ing] peripheral stem cell transplants" towards the end of the article, *id.* at 2, but McNeil nowhere suggests administering IDEC-C2B8 in combination with stem cell transplantation. *Id.* at 1-2; Ex. 2011, ¶ 135.

Moreover, McNeil answers none of the questions left unaddressed by Link: How would patients >60 years old respond to rituximab and CHOP? How about DLCL patients > 60 years old? How might patients respond to fewer than six doses of rituximab and CHOP? Was rituximab plus CHOP more efficacious than rituximab alone? Did rituximab and CHOP have overlapping toxicities? Would the risks of adding a stem cell transplantation regimen to a regimen of rituximab plus CHOP outweigh the potential benefits? *See* Ex. 2011, ¶¶ 136, 88-95.

McNeil reports that researchers had merely started a trial to explore the first question: How would patients >60 years old respond to rituximab and CHOP. McNeil discloses that "[r]esearchers in December launched a . . . phase III trial [that] will compare CHOP alone to CHOP plus the new monoclonal antibody IDEC-C2B8 (Rituxan)." Ex. 1003, 1; Ex. 2011, ¶¶ 91, 137. But McNeil provides no details about the study design, including how many cycles of CHOP would be used. Ex. 2011, ¶¶ 91, 137. Nor does McNeil report any results from this phase III trial, which reportedly was launched only two months earlier. *See* Ex. 1003, 1 (bearing the date "February 18, 1998" in the footer and noting that "[r]esearchers in December launched" the new trial).

Accordingly, a person of ordinary skill in the art would not have been motivated by McNeil to add rituximab to the three doses of CHOP in Moreau. Ex. 2011, ¶ 138.

Petitioner argues that McNeil discussed a need for alternatives to CHOP monotherapy and "suggested that one such 'alternative' to CHOP monotherapy in patients over 60 'could be CHOP plus the monoclonal antibody [rituximab]." Pet. 46-47. But even if true, that would not have provided a POSA with a motivation to add rituximab to the CHOP in Moreau, which was part of a line of treatment that further included a stem cell transplantation regimen (for patients who responded to the CHOP).

Moreover, McNeil reported that a trial of CHOP plus rituximab was already underway to determine whether it was, in fact, an alternative to CHOP monotherapy. Ex. 1003, 1. The fact that a trial was underway would not have motivated a person having ordinary skill in the art to undertake parallel study of rituximab and CHOP in elderly patients, let alone administer the rituximab in combination with a stem cell transplantation regimen. Ex. 2011, ¶ 139. McNeil offers no predictions regarding what the results of the randomized trial would be. *Id.* And potential therapies often have negative results in clinical trials. *Id.*; Ex. 2008, 26:15-18. Based on the principle Dr. Ozer affirmed at deposition, a POSA would have waited to determine that CHOP plus rituximab was better than CHOP

monotherapy before trying CHOP plus rituximab plus a stem cell transplantation regimen. Ex. 2008, 27:12-18.

According to Petitioner, "McNeil suggested that fewer cycles of CHOP chemotherapy (three cycles rather than the traditional six), combined with stem cell transplantation from the peripheral blood (rather than the bone marrow), was effective and well tolerated by patients over 60." Pet. 16. Similarly, Dr. Ozer stated that "McNeil reported on on-going trials in elderly patients, particularly those trials testing the efficacy of CHOP in combination with stem cell transplantation." Ex. 1002, ¶ 58. McNeil did no such thing. Both of these statements are inaccurate in multiple respects.

First, contrary to Petitioner's representation, McNeil did not disclose the use of CHOP combined with a stem cell transplantation regimen. As Dr. Ozer confirmed at deposition, "there's no description in McNeil of administering CHOP in combination with stem cell transplantation." Ex. 2008, 61:17-20; Ex. 2011, ¶¶ 95, 140.

Second, contrary to Petitioner's representation, McNeil did not disclose "fewer cycles of CHOP chemotherapy"—or any other chemotherapy—combined with stem cell transplantation, let alone "three cycles rather than the traditional six." Rather, McNeil described a peripheral stem cell transplant "approach that is combined with low-dose chemotherapy regimens." Ex. 1003, 2; Ex. 2011, ¶ 94.

Low-dose chemotherapy regimens did not use "fewer cycles" of chemotherapy. Rather, low-dose chemotherapy regimens use reduced amounts of chemotherapies in each dose. Ex. 2011, ¶ 94. Indeed, Dr. Ozer confirmed at deposition that "[r]educing the amount of chemotherapies in each cycle was referred to as using low dose chemotherapy regimens." Ex. 2008, 31:13-16; Ex. 2011, ¶ 94.

Third, contrary to Petitioner's representation, McNeil did not report that chemotherapy combined with stem cell transplantation "was effective and well tolerated by patients over 60." Rather, McNeil simply reported, without elaboration, that "[t]rials are under way at the University of Nebraska and the University of Texas M.D. Anderson Cancer Center in Houston where there have been *some* 'impressive responses.'" Ex. 1003, 2 (emphasis added). McNeil nowhere mentions effectiveness or tolerability.

Thus, Petitioner fails to establish that McNeil would have motivated a POSA to add rituximab to the three doses of CHOP in Moreau, prior to a possible stem cell transplantation regimen.

(iii) *Maloney Would Not Have Motivated A POSA To Add Rituximab To The CHOP In Moreau.*

Maloney reports a trial of rituximab in twenty patients with relapsed B-cell lymphoma. Ex. 1008, 5. Fifteen of the patients had low-grade lymphoma. *Id.* Five of the patients had intermediate-/high-grade lymphoma. *Id.* Two patients were

classified as IWF type "G," which corresponds to DLCL. *Id.* at 5 (Table 1); Ex. 2011, ¶ 96. Maloney does not report the ages of these patients. Ex. 2011, ¶ 96.

Maloney administered four weekly infusions of IDEC-C2B8 (rituximab) monotherapy to patients at one of three dose levels. Ex. 1008, 4. "No concomitant cancer chemotherapy, radiotherapy, hormonal therapy, or immunotherapy was allowed." *Id.* at 5; Ex. 2011, ¶ 97.

Maloney reports that of the twenty patients in the trial, "[t]wo patients were not assessable for efficacy," leaving eighteen. Ex. 1008, 7. "The overall response rate was 33%," with responses "noted in six of [the] 18 patients." *Id.* at 7-8. All six of the responses were in patients with low-grade NHL. *Id.* at 8 ("Six of 15 patients (40%) with low-grade histology responded with a PR."); Ex. 2011, ¶ 98. As Dr. Ozer confirmed at deposition, none of the DLCL patients responded. Ex. 2008, 53:15-22; Ex. 2011, ¶¶ 98, 141. Nor did any of the other patients with intermediate- or high-grade lymphomas. Ex. 2008, 53:23-25; Ex. 2011, ¶ 98.

Thus, Maloney is a study of rituximab monotherapy, and none of the DLCL patients in Maloney responded to the monotherapy. Ex. 1008, 8; Ex. 2008, 53:15-22; Ex. 2011, ¶ 141. Maloney does not even disclose administering CHOP and a stem cell transplantation regimen to a patient, let alone administering to the patient an anti-CD20 antibody in combination with a stem cell transplantation regimen.

Ex. 1008; Ex. 2011, ¶ 142. Like McNeil, Maloney answers none of the questions left unaddressed by Link. Ex. 2011, ¶¶ 143, 136.

Moreover, Maloney administered to patients four doses of rituximab on a weekly basis, not every 21 days, like "CHOP was usually administered," as Dr. Ozer confirms. Ex. 1002, ¶ 40; Ex. 2008, 28:23-25; Ex. 2011, ¶ 145. Petitioner does not articulate any reason why a reference disclosing administering rituximab once a week for four doses might have prompted a person having ordinary skill in the art to administer rituximab once every 21 days (or 28 days) for three doses. Ex. 2011, ¶ 145. Maloney nowhere discloses using less than four doses of rituximab. Ex. 1008.

Accordingly, Maloney would not have motivated a POSA to add rituximab to the three doses of CHOP in Moreau.

Petitioner argues that Maloney provides a motivation to add rituximab to the three doses of CHOP in Moreau because (i) Maloney states that rituximab "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;" and (ii) Maloney reports results "in patients heavily ***pretreated*** with chemotherapy, including aggressive regimens and ABMT." Ex. 1008, 10 (emphasis added). But this describes administration of rituximab only ***after*** the stem cell transplantation or recent chemotherapy pretreatment. Ex. 2011, ¶¶ 144, 99. The three doses of

CHOP in Moreau to which rituximab allegedly would have been added, however, were not administered to patients after stem cell transplantation or chemotherapy. *Id.* Moreover, the patients in Moreau were treatment-naïve, Ex. 2008, 49:4-6 (Dr. Ozer confirming that all of the patients in Moreau's "upfront study" "were treatment naïve"); Ex. 2011, ¶ 144, so they were not patients who were myelosuppressed due to recent chemotherapy, patients who had been treated with high-dose chemotherapy with ABMT, or patients heavily pretreated with chemotherapy, including aggressive regimens and ABMT, such that this purported teaching of Maloney would apply to them.

Thus, Petitioner fails to establish that Maloney would have motivated a POSA to add rituximab to the three doses of CHOP in Moreau.

(d) Petitioner Did Not Contend That Moreau Or Coiffier Would Have Motivated A POSA To Add Rituximab To The Three Doses Of CHOP In Moreau.

Petitioner did not contend that Moreau itself or Coiffier would have motivated a POSA to add rituximab to the three doses of CHOP in Moreau—and for good reason: neither do. Ex. 2011, ¶ 146.

(i) Moreau Itself Would Not Have Motivated A POSA To Add Rituximab To The CHOP In Moreau.

Moreau sought "to answer the question about the feasibility of PBSCT as front-line treatment up to the age of 65 years." Ex. 1007 at 1; Ex. 2011, ¶ 72.

Moreau simply concluded "that PBSCT can probably be performed in patients between 61 and 65 years of age" and "that patients with intermediate- or high-grade disseminated NHL should not be excluded from trials evaluating the role of ASCT as part of initial treatment." Ex. 1007, 3-4; Ex. 2011, ¶¶ 77-78, 147, 150.

Petitioner asserts that "[i]n late 1997," the year before Moreau was allegedly published, "the FDA approved Rituxan™, the commercial form of rituximab, for the treatment of patients with relapsed or refractory *low-grade* B-cell NHL." Pet. 19. And yet, nowhere does Moreau suggest, or even mention, adding rituximab (or anything else) to the three doses of CHOP. Ex. 2011, ¶ 148. Nor does Moreau suggest the possibility of testing rituximab in trials evaluating the role of stem cell transplantation as part of initial treatment, let alone rituximab in combination with stem cell transplantation regimen. *Id.*

Thus, a POSA would not have been motivated by Moreau itself to add rituximab to the three doses of CHOP. Petitioner does not contend otherwise. Ex. 2011, ¶ 149.

(ii) *Coiffier Would Not Have Motivated A POSA To Add Rituximab To The CHOP In Moreau.*

Coiffier studied rituximab monotherapy in "patients with diffuse large B-cell lymphoma (DLCL), mantle cell lymphoma (MCL), or other intermediate- or high-grade B cell lymphomas according to the Working Formulation." Ex. 1006, 1; Ex. 2011, ¶¶ 100, 151. These patients received eight doses of rituximab, not three.

Ex. 1006, 1. And Coiffier administered the eight doses of rituximab on a weekly basis, not every 21 days like CHOP was usually administered. Ex. 2011, ¶¶ 101, 151.

Coiffier did not identify any responders as >60 years old. Ex. 1006, 3; Ex. 2011, ¶¶ 102, 152. Like McNeil and Maloney, Coiffier answers none of the questions left unaddressed by Link. Ex. 2011, ¶ 153.

Petitioner relies on Coiffier's conclusion that "Rituximab has significant activity in DLCL and MCL patients and should be tested in combination with chemotherapy in such patients." Ex. 1006, 1. But Coiffier did not encourage testing rituximab and CHOP in the claimed DLCL patients >60 years old, let alone administering the rituximab in combination with stem cell transplantation. Ex. 1006; Ex. 2011, ¶ 154.

Petitioner contends that "Coiffier confirmed that rituximab was safe and effective in elderly patients with DLCL." Pet. 23; Ex. 2011, ¶ 156. But as explained above, Coiffier did not identify a single DLCL patient over 60 as a responder. Ex. 2011, ¶¶ 102-103, 152.

Accordingly, nothing in Coiffier would have motivated a POSA to add rituximab to the three doses of CHOP in Moreau. *Id.* at ¶ 155.

2. Petitioner Failed To Establish That Adding Rituximab To The Three Doses Of CHOP In Moreau Would Have Resulted In The Invention Of The Claims, As Properly Construed.

As discussed in the "Claim Construction" section above, the claims require the anti-CD20 antibody to be administered during a stem cell transplantation regimen. Ex. 2011, ¶¶ 110-111. Petitioner entirely failed to address whether a POSA would have had a reason or motivation to modify or combine Moreau, Link, McNeil, Maloney, and Coiffier to administer an anti-CD20 antibody and CHOP to a DLBCL patient >60 years old, wherein the anti-CD20 antibody is administered during a stem cell transplantation regimen. *See* Ex. 2011, ¶¶ 112, 114.

Petitioner contended that a POSA would have been motivated to add rituximab to the three doses of CHOP in the method of Moreau. Petitioner failed to establish any such motivation, as discussed above. *See* Section V.B.1. But even if it had, Petitioner never contended that adding rituximab to the three doses of CHOP in Moreau would have resulted in administering rituximab during a stem cell transplantation regimen. Accordingly, Petitioner failed to establish a prima facie case of obviousness. It is too late for Petitioner to try doing so now. The Board should confirm all claims.

C. Petitioner Failed To Establish That A POSA Would Have Had A Reasonable Expectation Of Success.

"An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art." *Amgen*, 580 F.3d at 1362. The reasonable expectation of success requirement "refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Cumberland Pharm. Inc. v. Mylan Institutional LLC*, 846 F.3d 1213, 1222 (Fed. Cir. 2017). "[T]he burden falls on the patent challenger to show . . . that a person of ordinary skill in the art would have had reason to . . . carry out the claimed process, and would have had a reasonable expectation of success in doing so." *Amgen*, 580 F.3d at 1362.

It is well-established that "medicinal treatment" is one of the "unpredictable arts." *In re Efthymiopoulos*, 839 F.3d 1375, 1380 (Fed. Cir. 2016). As Dr. Ozer confirmed at deposition, potential therapies "often have negative results in clinical trials." Ex. 2008, 26:15-18. "Either a combination or a drug [] is intolerable, or a combination or drug [] has no efficacy, or a combination or a drug [] has less efficacy than whatever is the standard." *Id.* at 26:19-23.

Petitioner fails to show that a POSA would have had a reasonable expectation of success in combining Moreau, Link, McNeil, Maloney, and Coiffier to arrive at the claimed invention.

The petition lacks any meaningful analysis of the "reasonable expectation of success" requirement. It mentions reasonable expectation of success only five times. Two of those times, the petition simply advances naked conclusions. Pet. 41 ("Indeed, a skilled artisan would have reasonably anticipated success in pursuing the therapy suggested by the prior art that ultimately became the claimed invention."); *id.* at 49 ("In sum, 'a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that [] skilled artisan would have had a reasonable expectation of success from doing so.'") (omission in original).

The other three times the petition mentions expectation of success, it simply argues that a POSA would have had a reasonable expectation of success because "Link teaches that the toxicity of rituximab does not overlap with the toxicity of CHOP therapy." Pet. 46; *see also* Pet. 28, 47. This argument fails for multiple reasons.

First, it is not true that "Link teaches that the toxicity of rituximab does not overlap with the toxicity of CHOP therapy." Pet. 46. As Dr. Ozer confirmed at deposition, "Link does not state that there is no overlap between the toxicity of Rituximab and the toxicities of CHOP therapy." Ex. 2008, 51:4-8. Even if it did, "Link did not study patients over 60," as Petitioner admits. Pet. 21. Thus, Link

simply did not collect any data regarding toxicities in the claimed population of DLCL patients >60 years old.

Second, Petitioner never established that success in "treating a patient with diffuse large cell lymphoma" with multiple therapies, as claimed, was simply defined by an absence of overlapping toxicities. Nor could it have, as that would have ignored the importance of the total level of toxicity, whether resulting from overlapping or non-overlapping toxicities. As Dr. Ozer confirmed at deposition, "the total toxicity associated with using multiple drugs together can be too high even if the toxicities of those individual drugs do not overlap." Ex. 2008, 25:15-19. Petitioner could not reasonably contend that a multiple-therapy regimen having unacceptable levels of total toxicity would have been considered successful by a POSA so long as the toxicities of those multiple therapies did not overlap.

Defining success simply as an absence of overlapping toxicities also would entirely ignore the importance of efficacy. Petitioner could not reasonably contend that so long as the toxicities of the multiple therapies did not overlap, a multiple-therapy regimen with no efficacy would have been considered by a POSA to be successful.

According to Petitioner, the problem facing a POSA "was whether new therapies would have improved prognosis for patients over 60 years." Pet. 40. But

Petitioner fails to adduce evidence that a POSA would have had a reasonable expectation of any such improved prognosis.

Petitioner fails even to establish a reasonable expectation of success in using rituximab and CHOP together in DLCL patients over 60 years old, let alone in such patients who receive stem cell transplantation therapy. As explained above, neither Coiffier nor Link—nor any of the other alleged prior art—reports successful treatment of DLCL patients >60 years old with rituximab alone, much less rituximab plus CHOP. *See* Section V.B.1. Indeed, Dr. Ozer confirmed at deposition that although Coiffier reports that some patients responded to rituximab monotherapy, "Coiffier does not identify any of those responders as greater than 60 years old." Ex. 2008, 55:1-4. Similarly, Dr. Ozer confirmed that "Link is an abstract that reports studying 31 patients" and "Link does not identify any of those patients as greater than 60 years old." *Id.* at 49:22-50:2.

Dr. Ozer's declaration in support of the petition contains even less discussion of reasonable expectation of success than the petition does. Dr. Ozer's declaration refers to "reasonable expectation of success" exactly twice. The first time is simply an acknowledgement that the law requires Petitioner to establish a reasonable expectation of success. Ex. 1002, ¶ 19. The second time is a naked, throwaway conclusion in a clause at the very end of a paragraph addressing an alleged motivation to combine. *See id.* at ¶ 89. Petitioner was required to include

evidence of a reasonable expectation of success as part of its prima facie case. *Amgen*, 580 F.3d at 1362 ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art."). Petitioner cannot cure this failure of proof by trying to submit such evidence now.

Petitioner contends that "it would have been obvious to a POSA to add rituximab to a reduced CHOP regimen—including one followed by PBSCT—to achieve the same efficacy as CHOP monotherapy but with less toxicity, or to add rituximab to the full number of CHOP cycles to achieve more efficacy without any added toxicity." Pet. 40-41. But Petitioner does not even come close to establishing that a POSA would have expected adding rituximab to the fewer-than-standard cycles of CHOP in Moreau would "achieve ***the same*** efficacy as CHOP monotherapy" in any patient, let alone in DLCL patients >60 years old. Pet. 41. Petitioner does not cite any prior art reference administering rituximab and fewer than six to eight cycles of CHOP, and nowhere does Dr. Ozer support Petitioner's assertion that such a regimen would have been expected to achieve the same efficacy as CHOP monotherapy.

Similarly, Petitioner does not come close to establishing that a POSA would have expected "add[ing] rituximab to the full number of CHOP cycles [would] achieve ***more*** efficacy" than CHOP monotherapy in DLCL patients >60 years old.

The only reference reporting results from administering rituximab and CHOP to any patients is Link, and Link would not have established any such expectation because it: (i) studied patients younger than 60 years old, and (ii) did not report results for DLCL patients as a group. Moreover, Link ultimately equivocated with respect to the patients it studied, concluding merely that rituximab and CHOP "***may*** offer higher response rates." Ex. 1005 at 5 (emphasis added). Such a conclusion would not have inspired in a POSA a reasonable expectation that rituximab and CHOP ***would*** offer higher response rates in an older patient population with a particular disease. Petitioner's proposed expert does not contend otherwise.

Even if "it would have been obvious to a POSA to add rituximab to a reduced CHOP regimen—including one followed by PBSCT—to achieve the same efficacy as CHOP monotherapy but with less toxicity, or to add rituximab to the full number of CHOP cycles to achieve more efficacy without any added toxicity," Pet. 40-41, the claimed invention would still not be obvious because the claims require not only administration of rituximab and CHOP, but also a stem cell transplantation regimen. Petitioner never established that a POSA would have had a reasonable expectation of success in administering rituximab and CHOP, followed by stem cell transplantation regimen (let alone in combination with a stem cell transplantation regimen), in DLCL patients >60 years old.

D. Petitioner Failed To Establish That Adding Rituximab To The Three Doses Of CHOP In Moreau Would Have Been Obvious To Try.

Petitioner argues that there were "a 'finite number of identified, predictable solutions' to the known problem of treating DLCL patients over 60 years old more effectively without increasing toxicity," and therefore the claimed invention was "obvious to try." Pet. 48. The Board should reject this argument because Petitioner failed to show that the claimed invention was even one of a finite number of identified solutions, let alone a predictable one.

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

Quoting parts of *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009), Petitioner states that "[a] set of solutions is . . . 'finite' where the prior art thereby reduces the options to a set that is 'small or easily traversed.'" Pet. 48-49. But Petitioner never analyzes the prior art to identify the available options. Rather, Petitioner simply works backward and selects the therapies of the claims themselves as "the available options: CHOP, rituximab, and stem cell transplantation." Pet. 49; Ex. 2011. Alleging that a claimed invention is drawn from one of a "finite number of predictable solutions" without "sufficient evidence or explanation" justifying the number exposes the allegation as "simply a hindsight statement based on the invention described in the [] patent." *Becton,*

Dickinson & Co. v. B. Braun Melsungen AG, No. IPR2017-01585, Paper No. 8, at 19-20 (P.T.A.B. Dec. 15, 2017).

Even Petitioner's own references identify additional options. For example, as Dr. Ozer confirmed at deposition, "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. 2008, 43:25-44:4; Ex. 1003, 2; Ex. 2011, ¶¶ 160-161. Dr. Ozer also confirmed that "McNeil identifies the chemotherapy CTVP, cyclophosphamide, tenopside [sic], and pirarubicin as a potential alternative to CHOP." Ex. 2008, 44:6-9; Ex. 1003, 2. Moreover, according to Dr. Ozer, "other chemotherapeutic regimens available at the time of the claimed invention included m-BACOD, ProMACE-CytaBOM, and MACOP-B." Ex. 2008, 29:5-9; Ex. 1002, ¶ 41; Ex. 2011, ¶¶ 162-63. In addition to chemotherapy, a POSA would also have known that radiation therapy, for example, was an available option to treat DLCL at that time. Ex. 2011, ¶ 164; Ex. 1013, 10.

Notably, Dr. Ozer's declaration in support of the petition nowhere supports Petitioner's position that "the available options" were limited to CHOP, rituximab, and stem cell transplantation. Ex. 2011, ¶ 165. Dr. Ozer simply asserted that "rituximab, CHOP, and stem cell transplantation were three identified, known solutions to the problem of DLCL in all its forms—including in the elderly and

those with bone marrow involvement." Ex. 1002, ¶ 98; Ex. 2011, ¶ 157. He did not assert or imply that those were the only options.

In any event, Dr. Ozer did not justify his position that each of rituximab and stem cell transplantation was a "known solution[]" to treating DLCL patients >60 years old. As Dr. Kahl explains, rituximab had not risen to the level of a known solution for DLCL as of the priority date—either in patients generally or in the elderly. Ex. 2011, ¶ 158. Neither Link nor Coiffier, for example, identified any results from using rituximab to treat elderly DLCL patients, and no DLCL patients in Maloney responded to rituximab. *Id.*; *see* Sections V.B.1(c)(i), V.B.1(c)(iii), and V.B.1(d)(ii). Neither would a person having ordinary skill in the art have considered stem cell transplantation to have been a known solution for treating DLCL in elderly patients as of the priority date. Ex. 2011, ¶ 159. Indeed, Moreau states that "ASCT [autologous stem cell transplantation] is usually restricted to patients aged ≤60 years." Ex. 1007, 1.

Accordingly, the Board should reject Petitioner's artificially narrow universe of available options. The evidence shows that the options were not limited to CHOP, rituximab, and stem cell transplantation.

In any event, Petitioner focuses on individual elements of the invention as available options. But an obvious-to-try analysis focuses on 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) (emphasis added). Petitioner never even contends that the prior art identified as a possible treatment for DLCL patients >60 years old administering CHOP and an anti-CD20 antibody in combination with a stem cell transplantation regimen. If Petitioner's argument is that prior art would have prompted a POSA to piece such a treatment together, then Petitioner is making a motivation-to-combine argument, not an obvious-to-try argument. And that motivation-to-combine argument fails for the reasons discussed above. *See* Section V.B.1.

Petitioner argues that "it was obvious to combine rituximab, which destroys cancerous B-cells by attaching to the CD20 antigens expressed on those cells, and CHOP, a form of chemotherapy, because of their separate mechanisms of action." Pet. 49. Petitioner cites *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.* for the proposition that "[w]here '[i]t was apparently well-known in the art that two drugs having different mechanisms for attacking [the disease] may be more effective than one,' it is at minimum 'obvious to try combination therapy.'" Pet. 49. But in *Novo Nordisk*, the two drugs at issue—an insulin secretagogue and an insulin sensitizer—attacked diabetes in different ways. *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1355 (Fed. Cir. 2013). The insulin secretagogue worked "by stimulating insulin release from pancreatic beta cells," whereas the insulin sensitizer worked to "reduce insulin resistance by acting on the

liver to reduce glucose production and thereby improv[e] insulin sensitivity in muscle and fat tissues." *Id.* Here, Petitioner did not submit evidence that rituximab and CHOP attack DLCL in different ways.

2. Petitioner Failed To Establish That The Claimed Invention Was Predictable

Petitioner not only failed to show that the claimed invention was one of a finite number of identified solutions, it failed to show that any such solutions were predictable.

The Federal Circuit has observed that "in the medical arts potential solutions are less likely to be genuinely predictable as compared with other arts such as the mechanical devices in *KSR*." *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. Inc., USA*, 748 F.3d 1354, 1360 (Fed. Cir. 2014) (internal citations and quotation marks omitted). As noted above, it is well-established that "medicinal treatment" is one of the "unpredictable arts." *In re Efthymiopoulos*, 839 F.3d at 1380.

Petitioner did not even attempt to show that the claimed invention was predictable. Nor did Dr. Ozer opine that the claimed invention was predictable. Ex. 2011, ¶ 165.

"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) (emphasis added). Petitioner failed to establish a reasonable expectation of success, as discussed above. *See* Section V.C.

E. Additional Reasons Why A POSA Would Not Have Found Obvious The Difference Between Claim 4 And The Prior Art

The differences between claim 4, which depends on claim 1, and the alleged prior art would not have been obvious for all of the reasons discussed in Section V. above. Ex. 2011, ¶ 166.

Further, the differences between claim 4 and the alleged prior art would not have been obvious because claim 4 recites a method of treating a patient with DLCL according to "[t]he method of claim 1," Ex. 1001, 8:37-38, "wherein the lymphoma is accompanied by bone marrow involvement." *Id.* at 8:49-50; Ex. 2011, ¶ 167.

Petitioner states that Claim 4 is obvious because "Maloney reported tumor responses 'in peripheral blood, *bone marrow* (BM), spleen, bulky lymph nodes, and extranodal sites, and in patients who had relapsed following high-dose myeloablative chemotherapy.'" Pet. 50 (emphasis in original). Petitioner asserts that "Maloney thus taught a POSA that adding rituximab to CHOP therapy could successfully treat patients with cancerous cells in the bone marrow." *Id.* at 50-51. But as discussed above in Section V.B.2(c), none of the DLCL patients—or any other intermediate- or high-grade lymphoma patients—in Maloney responded to treatment with rituximab. Ex. 1008, 7-8; Ex. 2011, ¶¶ 168, 98. Nor did Maloney

report the ages of any patients who exhibited tumor responses in their bone marrow. Ex. 1008, 7-8; Ex. 2011, ¶ 168.

Petitioner's expert alleges that "[t]here is nothing atypical about lymphoma accompanied by bone marrow involvement, and certainly nothing that requires unique treatment." Ex. 1002, ¶ 97. But Maloney did not even report success in any DLCL patients without bone marrow involvement, let alone DLCL patients >60 years old with bone marrow involvement, as claimed. Ex. 2011, ¶¶ 169, 96, 98. For these additional reasons, claim 4 would not have been obvious over the Maloney reference. *Id.* at ¶ 170.

F. The Board Should Reject Petitioner's "Applicant-Admitted Prior Art" Argument

Petitioner argues that an excerpt from the '873 patent specification constitutes "applicant admitted prior art." Pet. 43. Even if the specification stated that something was in the prior art, such a statement would not be entitled to consideration here because "applicant-admitted prior art" is not a prior art patent or printed publication within the meaning of § 102 and thus cannot be used as a basis upon which to cancel claims in an IPR. *LG Elecs. Inc. v. Core Wireless Licensing S.A.R.L.,* No. IPR2015-01987, Paper No. 7 at 18 (P.T.A.B. Mar. 24, 2016) (IPR challenge based on AAPA "does not identify any patents or printed publications, [and thus] fails to comply with Section 311(b) or Rule 42.104(b)(4)."); *Kingbright Elecs. Co. v. Cree, Inc.*, No. IPR2015-00741, 2015 WL 5028023, at *4 (P.T.A.B.

Aug. 20, 2015) ("[W]e reject Petitioner's asserted ground relying solely on [] alleged 'AAPA' as not based on a prior art patent or printed publication."); *see also* 35 U.S.C. § 311(b).

Petitioner's citation to *Ex parte Xintian E. Lin & Qinghua Li*, No. 2015-7034, 2016 WL 6560248, at *1 (P.T.A.B. Nov. 2, 2016) in support of its argument, does not help it here. *Ex parte Lin & Li* was an ex parte appeal and thus did not (and could not) address the question of whether alleged applicant-admitted prior art can override statutory limitations on the Board's jurisdiction to consider materials other than patents and printed publications in IPR proceedings.[9] See 35 U.S.C. § 311(b); *Kingbright*, 2015 WL 5028023, at *4. Petitioner offers no authority suggesting AAPA can be used at all in an IPR, much less any sound basis to disregard section 311(b) and the Board's holdings in Kingbright and LG Electronics.

Even if the purported "applicant-admitted prior art" could properly be considered, the cited material fails to mention, for example: (i) CHOP; (ii) DLCL; or (iii) elderly patients. Thus, the purported applicant-admitted prior art would not cure any of the deficiencies in the instituted ground even if the Board considered it.

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

VI. CONCLUSION

The Board should reject Petitioner's obviousness arguments and confirm all of the challenged claims.

Dated: February 26, 2018

Respectfully submitted,

/s/ Michael R. 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 13,744 words as counted by the word-processing program used to generate the brief. This total does not include the tables of contents and authorities, the caption page, table of exhibits, certificate of service, or this certificate of word count.

Dated: February 26, 2018

Respectfully submitted,

/s/ Susan Langworthy
Susan Langworthy

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. 42.6, the undersigned certifies that on February 26, 2018, a copy of **BIOGEN, INC.'S PATENT OWNER RESPONSE** and **EXHIBITS 2002-2012** were served by electronic mail upon the following:

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