

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Boehringer Ingelheim International GmbH and
Boehringer Ingelheim Pharmaceuticals, Inc.
Petitioner,

v.

Biogen Idec, Inc.
Patent Owner

Patent No. 8,329,172 B2
Issued: December 11, 2012
Filed: August 18, 2007
Inventor: Antonio J. Grillo-López

Title: COMBINATION THERAPIES FOR B-CELL LYMPHOMAS
COMPRISING ADMINISTRATION OF ANTI-CD20 ANTIBODY

Inter Partes Review No. TBD

PETITION FOR INTER PARTES REVIEW

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I. PRELIMINARY STATEMENT

The challenged, and only, claim of U.S. Patent No. 8,329,172 (“the ’172 patent”) (Ex. 1001) relates to a method of treating low-grade B-cell non-Hodgkin’s lymphoma (sometimes referred to as “LG-NHL”) by administering two different agents—CVP and rituximab— both of which were known and used to treat LG-NHL long before the earliest priority date of the ’172 patent. CVP (a/k/a COP)¹ is a combination chemotherapy regimen that traditionally had been used for the treatment of LG-NHL. Rituximab is an antibody that had already been FDA approved to treat LG-NHL, and had been marketed under the tradename RITUXAN®. The claim is generally directed to administering CVP therapy to which a patient responds, followed by administrations of rituximab every 6 months, so as to provide maintenance therapy for 2 years.

The precise method claimed had been described in an anticipatory printed publication—ECOG 1496 (Ex. 1003)—more than one year before the earliest priority date to which the ’172 patent is entitled. ECOG 1496 is the protocol for a clinical trial conducted by the Eastern Cooperative Oncology Group (ECOG), a well-known organization that is publicly supported by the National Cancer

¹ CVP is a combination of the drugs cyclophosphamide, vincristine, and prednisone. Because the drug vincristine is also known as oncovin, CVP therapy is also sometimes referred to by the acronym “COP.”

Institute (“NCI”) of the U.S. National Institutes of Health. ECOG is a cooperative group made up of a network of physicians and researchers at numerous private and public institutions who are engaged in oncology research, including clinical trials. The protocols of, and results obtained from, clinical trials conducted by ECOG are publicly available and disseminated. ECOG 1496 is one such publication.

Each element of the challenged claim had also been extensively discussed in other literature published more than one year before the earliest priority date of the ’172 patent. For example, ECOG 4494 (Ex. 1004), another clinical trial protocol published by ECOG, and McNeil (Ex.1005), both described the use of a similar chemotherapy combination (CHOP), followed by the precise rituximab maintenance therapy recited in the claim, to treat non-Hodgkin’s lymphoma. CHOP is identical to the CVP chemotherapy recited in the challenged patent claim, except that it has one additional ingredient, hydroxydaunorubicin—the “H” in CHOP, which was known to be toxic and not beneficial for the treatment of LG-NHL.

McLaughlin (Ex.1009) is acknowledged by the patent owner, Biogen Idec, as having successfully provided the foundation for, and encouraged the use of, the patent’s claimed method of using rituximab maintenance therapy for the treatment of LG-NHL. Specifically, Biogen Idec states on its website for RITUXAN® that “B-cell depletion observed in the McLaughlin trial *formed the basis* for the ECOG

1496 dosing strategy following first-line CVP induction in low-grade NHL.” (emphasis added). The ECOG 1496 dosing strategy for which McLaughlin “formed the basis” is the precise dosing strategy of claim 1 of the ’172 patent. Indeed, McLaughlin strongly encouraged the treatment of LG-NHL by using rituximab maintenance therapy following prior chemotherapy, including CVP. It further shows that the standard course of rituximab therapy is effective to deplete B-cells for at least 6 months, the same interval between administrations of rituximab maintenance therapy that is recited in claim 1.

Other prior art encouraged the use of biologic therapeutics (of which rituximab is an example) as maintenance therapy for as long as possible, including for two years or more, following CVP therapy for the treatment of LG-NHL (*see, e.g.,* Unterhalt 1996 (Ex. 1006)). And still other publications describe the use of CVP to treat a form of LG-NHL, followed by multiple courses of rituximab therapy (*see, e.g.,* 1997 FDA Transcript (Ex. 1007)).

All the elements of the single ’172 patent claim were thus well known to a person of ordinary skill, who had a strong reason to combine them. Among other things, encouraging data from studies where biologic therapeutics (such as interferon²) were used as maintenance therapy, following CVP therapy, for the

² Interferon is a hormone made by white blood cells to stimulate the immune system.

treatment of LG-NHL, provided those of ordinary skill with much more than a reasonable expectation of success. This was particularly the case given rituximab's well-known advantages over other such biologic therapeutics, including rituximab's better toxicity profile. Ex. 1002 at ¶¶ 65-69.³

Notably, publications disclosing maintenance therapy for the treatment of LG-NHL were not cited during prosecution of the '172 patent. Such publications, however, provide the foundation for the current petition. Indeed, in Europe, the patentee surrendered a claim similar to the '172 patent claim in light of prior art publications that discussed maintenance therapy for the treatment of LG-NHL with various biologics including interferon and rituximab. Ex. 1057.

For all the reasons discussed herein, and in the supporting declaration by Dr. Michael L. Grossbard (Ex. 1002), claim 1 of the '172 patent should be held unpatentable as anticipated and/or obvious.

II. MANDATORY NOTICES

A. Real Parties-in-Interest or Privies

The real parties in interest are: (i) Boehringer Ingelheim Pharmaceuticals, Inc., located at 900 Ridgebury Road, Ridgefield, CT 06877; and (ii) Boehringer Ingelheim International GmbH, located at Binger Strasse 173, Ingelheim am Rhein, Germany 55216 (collectively, "Boehringer" or "Petitioner")

³ All page numbers cited herein refer to the original pagination of the exhibits.

B. Related Matters

Simultaneously with this petition, Petitioner has filed petitions for *Inter Partes* Review against United States Patent Nos. 7,820,161 and 7,976,838. The following patents and patent applications may claim the benefit of the priority of the filing date of U.S. Patent No. 8,329,172: 6,455,043, USSN 13/524837, USSN 13/868753, USSN 14/070256, and USSN 13/524896.

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III. CERTIFICATION OF GROUNDS FOR STANDING

Petitioner certifies pursuant to 37 C.F.R. § 42.104(a) that the patent for which review is sought is available for *inter partes* review and that Petitioner is not

barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this petition.

IV. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED

Petitioner challenges claim 1, the only issued claim of the '172 patent (Ex. 1001), as unpatentable under 35 U.S.C. §§ 102 and 103 on the specific grounds set forth in Section IX below. This petition is supported by the Declaration of Michael L. Grossbard, M.D. (Ex.1002). The petition and supporting declaration show that there is a reasonable likelihood that Petitioner will prevail with respect to the challenged claim. *See* 35 U.S.C. § 314(a).

V. SUMMARY OF THE '172 PATENT AND PROSECUTION HISTORY

The '172 patent names Antonio J. Grillo-López as the sole inventor and Biogen Idec as the assignee. Ex. 1001. The '172 patent issued on December 11, 2012 from application ser. no. 11/840,956 (Ex. 1058, “the '956 application”), which was filed on August 18, 2007 but claimed priority, through a series of continuation applications, to U.S. patent application ser. no. 09/372,202 (“the '202 application”), filed on August 11, 1999. The '202 application claimed priority to provisional application ser. no. 60/096,180 (Ex. 1059, “the '180 provisional application”), which was filed even earlier on August 11, 1998. As explained below, however, the '180 provisional application does not provide adequate § 112 support for the '172 patent’s issued claim. Hence, August 11, 1999, the filing date

of the '202 Application, is the earliest possible effective filing date for claim 1 of the '172 patent.

Any publication prior to August 11, 1998 therefore qualifies as prior art under 35 U.S.C. §102(b) (“the 102(b) date”).

A. The '172 Patent's Issued Claim

Claim 1, the '172 patent's only claim, recites a method of treating LG-NHL patients with two known LG-NHL treatments, (i) CVP chemotherapy and (ii) rituximab. The claim reads as follows (emphasis added):

1. A method of treating low grade B-cell non-Hodgkin's lymphoma in a human patient comprising **administering to the patient chemotherapy consisting of CVP therapy** to which the patient responds, **followed by rituximab maintenance therapy**, wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m² **every 6 months, and wherein the maintenance therapy is provided for 2 years.**⁴

The claim's recited schedule of four weekly doses of 375 mg/m² had already been established as the recommended dosing schedule for RITUXAN® at least as early as RITUXAN®'s 1997 label. Ex. 1008; *see* section VIII C.3 below.

⁴ Except as noted, all emphases in quotations have been added.

B. The Claims Upon Which Issued Claim 1 of the '172 Patent is Based

Claim 1 of the '172 patent originated from claims 41-43, which were added to the '956 application on October 31, 2007, *more than eight years after* the '202 application had been filed. *See* Ex. 1060 at 4. Those new claims read:

41. A method of treating low grade B-cell non-Hodgkin's lymphoma in a human patient comprising administering to the patient CVP therapy followed by rituximab maintenance therapy, wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m² every 6 months.

42. A method according to claim 42, wherein the patient exhibits a response to the CVP therapy.

43. A method according to claim 42, wherein the maintenance therapy is provided for 2 years.

Claim 41 was later amended to incorporate the elements of claims 42 and 43, and subsequently issued as claim 1 of the '172 patent. *See* Ex. 1061 at 2, 5.

C. Claim 1 Is Not Entitled to the '180 Provisional Application's Early Filing Date

When the applicants added new claims 41-43 they did not cite for support to any disclosure in the earlier '180 provisional application. Instead, for support, they referenced "page 28, lines 16-21" of the '956 application, Ex. 1060 at 5, which corresponds to the passage at column 13, lines 8-16 of the issued '172 patent and reads as follows:

A Phase III study conducted by ECOG in patients with low-grade NHL is comparing the combination of cyclophosphamide and fludarabine (Arm A) with standard CVP therapy (Arm B). In the randomization to Arm A or Arm B, patients are stratified by age, tumor burden, histology, and B symptoms. Responders in both arms will undergo a second randomization to Rituximab maintenance therapy (375 mg/m² weekly times 4 every 6 months for 2 years (Arm C) or to observation (Arm D).

The '180 provisional application does not contain the above passage. In fact, the '180 provisional application (Ex. 1059) consists entirely of a compilation of a published article, several abstracts and a poster presentation, followed by two pages of claims. Nothing in that compilation describes the specific combination claimed in the '172 patent.

Accordingly, the '180 provisional application does not provide adequate § 112 support for claims 41-43 presented in the '956 application and, for at least the same reasons, it does not provide adequate § 112 support for issued claim 1 of the '172 patent. The patent examiner agreed, noting that “[t]he claimed inventions [including then-pending claims 41-43] are not disclosed in parent application 60/096180. Therefore, regarding the application of prior art, the instant application is not entitled to priority to said application.” Ex. 1062 at 4. The applicants never traversed that statement and, by not doing so, effectively conceded the Office’s position on priority. In view of this, the earliest priority date to which claim 1 of

the '172 patent is entitled is the filing date of the '202 application—August 11, 1999. Any publication on or before August 11, 1998, for example, is therefore prior art under § 102(b).

D. Prosecution of the Challenged Claim Did Not Address Prior Art That Discussed “Maintenance Therapy” Following Chemotherapy to Treat Non-Hodgkins Lymphoma

Claims 41-43 were rejected as obvious during prosecution of the '956 Application before being finally allowed to issue as claim 1 of the '172 patent. In contrast to the art upon which this petition is based, however, none of the art cited by the Examiner during prosecution discusses the use of “maintenance therapy” following chemotherapy (*e.g.*, CVP or CHOP) to treat non-Hodgkins lymphoma, much less low grade non-Hodgkins lymphoma.

For example, on February 29, 2012, in the last rejection of claim 41 (which is the predecessor to the challenged claim) before allowance, the Examiner cited two different combinations of references as the bases for obviousness rejections. Ex. 1063 at 7-11. In each combination of references, the Examiner relies on “IDEC Pharmaceuticals Press Release (12/9/96)” as the primary reference. As characterized by the Examiner, the press release

discloses that it is desirable to use rituximab in combination with other anti-cancer treatments. Said reference does not disclose use of rituximab in combination with CVP (aka COP).

Id. at 7. None of the cited references were described as discussing maintenance therapy. Indeed, in its May 22, 2012 Response, the applicant stated that a “prima facie case for obviousness has not been made out as to claim 41,” and further noted that “[t]he Examiner has not shown how the combined art teaches the aspects of claim 41 bolded above [including maintenance therapy].” Ex. 1064 at 4.

In contrast to the references cited during prosecution, this petition cites a number of references that describe maintenance therapy for treating NHL, including at least the following § 102(b) prior art—ECOG 1496 (Ex. 1003); ECOG 4494 (Ex.1004); McNeil (Ex.1005); Unterhalt 1996 (Ex.1006); and McLaughlin (Ex.1009).

E. Patentee’s Failed Attempt to Demonstrate Unexpected Results

In its May 22, 2012 Response, the applicant attempted to use Hochster to demonstrate unexpected results associated with the claimed method. Ex. 1064 at 7-10. However, as discussed in greater detail below (*see* Section X), the Examiner did not rely on, and the applicant did not attempt to demonstrate unexpected results over, prior art that described the use of maintenance therapy to treat LG-NHL. Indeed, such prior art shows that the results that the applicant characterizes as “unexpected” were, in fact, entirely expected. Ex.1002 at ¶¶ 113-121, 137-140. In any event, the results relied upon by the applicant are otherwise insufficient to impart patentability to the ’172 patent claim.

VI. CLAIM CONSTRUCTION

Because the '172 patent has not yet expired, the challenged claim should be given its broadest reasonable construction in light of the specification of the patent. 37 C.F.R. § 42.100(b).

A. “A method of treating low grade B-cell non-Hodgkin’s lymphoma in a human patient comprising”

Under the broadest reasonable construction standard, the “comprising” language of the claim encompasses, among other things, additional forms of treatment that may be administered to the patient as long as the patient is administered “chemotherapy consisting of CVP therapy to which the patient responds followed by rituximab maintenance therapy”

B. “administering to the patient chemotherapy consisting of CVP therapy to which the patient responds.”

Under the broadest reasonable construction standard, “chemotherapy consisting of CVP” means that the chemotherapy to which the patient responds, and which is followed by rituximab maintenance therapy, must be CVP. A patient who responds to “chemotherapy consisting of CVP” will have a response, including, for example, a complete response (CR) or a partial response (PR). Ex.1002 at ¶¶ 29-30, 38-39. When a patient has a complete response or complete remission (CR), the patient will have only minimal residual disease (MRD). *Id.* at ¶¶ 29, 57. When a patient has a partial response or partial remission (PR), the patient will have a substantially reduced tumor burden. *Id.* at ¶ 29. A patient with a

CR or PR will have a lower tumor burden relative to that which existed prior to the CVP chemotherapy. *Id.* at ¶¶ 29-30,38-39. The specification is consistent with this definition and explains that a patient who responds to CVP can have a response that includes a complete response (CR) or a partial response (PR):

Complete response required the regression of all lymph nodes to $<1 \times 1$ cm² demonstrated on two occasions at least 28 days apart on neck, chest abdomen, and pelvic CT scans, resolution of all symptoms and signs of lymphoma, and normalization of bone marrow, liver, and spleen. Partial response required a $\geq 50\%$ decrease in the sum of the products of perpendicular measurements of lesions without any evidence of progressive disease for at least 28 days. Patients who did not achieve a CR or PR were considered non-responders, even if a net decrease ($>50\%$) of measurable disease was observed.

Ex. 1001 at col. 9, lines 14-25.

C. “followed by rituximab maintenance therapy”

“Followed by” means that the “rituximab maintenance therapy” is administered at any time after the patient has responded to the chemotherapy consisting of CVP therapy, for example, after a CR or PR. Ex. 1002 at ¶ 62. “Rituximab” refers to the chimeric, anti-CD20 antibody also known as C2B8, for example. An example of such an antibody is RITUXAN®, which has been commercially marketed since at least 1997. Ex. 1001 at col. 1, lines 47-50 and col. 2, lines 59-60.

“Maintenance therapy” is not specifically defined in the ’172 patent. One of ordinary skill in the art would understand that “maintenance therapy” means treating a patient who has responded to “chemotherapy consisting of CVP” for the purpose of treating the MRD (for patients who responded with CR), prolonging the remission and/or preventing relapse. Ex. 1002 at ¶¶ 32, 42, 113-114. In the context of claim 1, “maintenance therapy” refers to administering rituximab after “chemotherapy consisting of CVP” for the purpose of treating the patient’s MRD (for patients who responded with CR), prolonging remission, and/or to prevent relapse. *Id.* This is consistent with statements made in prior art publications. *See* Ex. 1030 at 613 (“The aim [of BCG maintenance] was to control, after complete remission, the residual and undetectable lymphoma cells”); Ex. 1029 at 96 (“BCG seems useful as maintenance treatment in preventing relapse in all varieties of non-Hodgkin's lymphomas”); Ex. 1033 at Abstract (“The best results have been reported when IFN [interferon] was used as maintenance therapy in patients with minimal residual disease or complete remission”); Ex. 1033 at 154 (“Because relapse remains as the most important problem in patients with low-grade lymphoma, IFN [interferon] has been tested as a maintenance therapy in patients who have achieved CR or a good partial response (GPR)”); Ex. 1065 at 1163, col. 1 (“We and others are conducting studies on the role of maintenance therapy in prolonging remission in low grade NHL.”). The foregoing interpretation is also

consistent with the patentee's statements, during prosecution, arguing that the specification teaches maintenance therapy. *See, e.g.*, Ex. 1066 at 5 (“The benefits of such ‘sequential’ treatment regimes for prolonging remission or preventing relapse were disclosed . . . Thus, the specification read as a whole clearly described the presently claimed invention, including ‘maintenance therapy’ as in claim 41....”). In other words, the applicants associated “maintenance therapy” with prolonging remission or preventing relapse.

D. “wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m² every 6 months, and wherein the maintenance therapy is provided for 2 years.”

According to the 1997 FDA label for RITUXAN®, the standard course of rituximab therapy for treating LG-NHL is four weekly administrations at a dose of 375 mg/m² each. Ex. 1008 at 2, col. 1. Hence, according to the '172 patent claim, a course of rituximab maintenance therapy is provided every 6 months and must continue for at least two years, but can continue for a longer period of time due to the “comprising” transition language of the claim.

VII. LEVEL OF ORDINARY SKILL

LG-NHL is a chronic, incurable cancer that has been the subject of substantial research and published literature as seen from the numerous publications cited in the '172 patent. *See* Ex. 1002 at ¶ 35. Many doctors in the field participate in clinical trials involving new drugs and methods of treatment.

For this reason, hematologists and oncologists tend to be well informed about current trends and developing therapies for treating LG-NHL. *Id.* This was true in the 1990s and remains true today. *Id.*

In light of the specification, the references of record, and other available evidence, a person of ordinary skill at the time of the invention would have been a practicing hematologist, oncologist, and/or medical researcher who understood the pathophysiology of NHL diseases and was knowledgeable about methods for treating NHL patients through experience in treating such patients and/or the medical literature. *See Id.* at ¶ 36. For convenience, persons having this ordinary level of skill are sometimes referred to as “oncologists” in this petition.

VIII. THE STATE OF THE PRIOR ART

A. Chemotherapy for Low Grade Non-Hodgkin’s B-cell Lymphoma

B-cell lymphoma is a malignant disease characterized by uncontrolled growth of B-cells. B-cells, which are also known as “B lymphocytes,” are white blood cells that secrete antibodies when they mature. Non-Hodgkin’s lymphoma (“NHL”) is a type of B-cell lymphoma. Low grade or “indolent” NHL grows more slowly than high and intermediate grade lymphomas, which are also referred to as “aggressive” lymphomas. Low grade NHL often affects follicular B-cells in the lymph nodes. Ex. 1002 at ¶¶ 51-54.

Chemotherapeutic drugs that target rapidly dividing cells are used to treat malignant diseases such as NHL. Ex. 1002 at ¶ 40. One common strategy is to use a combination of drugs with different mechanisms of action in order to increase efficacy by attacking multiple targets found in malignant cells and reduce the chance of developing of drug-resistant cells. Two closely related chemotherapy regimens were considered during prosecution of the '172 patent. *Id.* at ¶ 41. CVP is a combination of the drugs cyclophosphamide, vincristine, and prednisone. Because the drug vincristine is also known as oncovin, CVP therapy is also sometimes referred to by the acronym “COP.” CHOP is another chemotherapeutic regimen that uses the same three drugs as CVP but, in addition, uses a fourth drug called hydroxydaunorubicin — the “H” in CHOP. Chemotherapy drugs, including those used in CVP and CHOP therapies, are known to have a variety of toxic side effects. Thus, oncologists must strike an appropriate balance between activity and toxicity in order to effectively treat the disease with tolerable side-effects. Prior to the 102(b) date, CHOP was the treatment of first choice for more aggressive, higher-grade lymphomas, and moderate intensity therapies such as CVP were preferentially used to treat low grade lymphomas. *Id.* at ¶ 55; Ex. 1011 at abstract and 1243. This remains true today.

The primary goal of chemotherapy is to drive cancer into remission. But chemotherapy rarely kills all of the billions of malignant cells that were present at

the start of treatment. Thus, even patients who appear to be in complete remission usually have “minimal residual disease” in the form of a relatively small number of malignant cells that can only be detected with highly sensitive molecular diagnostic techniques, such as PCR. Ex. 1002 at ¶¶ 57-59. Relapse occurs when these cells start growing again, leading to a recurrence of the disease. *Id.* at ¶ 57. Relapse may trigger the start of another course of chemotherapy with its toxic side-effects, and enhance the possibility that the cancer cells will develop resistance to chemotherapy. *Id.* at ¶ 61.

It was widely understood for at least 10 years before the priority date of the '172 patent that the malignant B-cells of LG-NHL are very difficult to completely eliminate. For example, Al-Ismail noted in 1987 that:

It is perhaps a misnomer to use the terms ‘favourable histology’ or ‘good prognosis’ for patients with low grade lymphoma as they are a group of incurable diseases. Although they are highly responsive to a variety of treatment programmes, their relapse rate remains high.

Ex. 1024 at 1382. As a result, treatment of LG-NHL was characterized by repeated cycles of induction, remission and relapse, followed some period later by death. Periods of remission would become shorter over time, while periods of relapse would become longer as remaining cancerous cells became resistant to subsequent, and increasingly more aggressive, courses of treatment. In end stages of LG-NHL, the cancer typically prevailed and the patient died. Accordingly, before the '172

patent's priority date, oncologists, were motivated to find ways to prolong the periods of remission when treating LG-NHL. Ex. 1002 at ¶¶ 60-61.

B. Maintenance therapy for LG-NHL

Since at least 1976, maintenance therapy has been used to treat the residual disease after chemotherapy, surgery, or radiation therapy. *See* Ex. 1012 at 63-64. The therapy that precedes maintenance therapy is sometimes referred to as “induction” therapy. Ex. 1002 at ¶ 40. Maintenance therapy for LG-NHL was first attempted using chemotherapeutic drugs, *See* Exs. 1012 and 1025, but this approach was relatively toxic and did not prolong survival. Greater success was obtained using the immunomodulatory agents, such as interferon, as maintenance therapy.

1. Maintenance therapy with interferon

Interferon- α (“IFN”), like rituximab, is a biological response modifier (“BRM”) that has been used in combination with chemotherapy to treat LG-NHL. Ex. 1002 at ¶ 65. Interferon is a hormone made by white blood cells to stimulate the immune system. Multiple clinical trials have shown that interferon maintenance therapy following chemotherapy can prolong progression-free survival. Ex. 1002 at ¶¶ 66, 140. For example, Aviles published a study entitled “Interferon Alpha 2b as Maintenance Therapy in Low Grade Malignant Lymphoma Improves Duration of Remission and Survival” (Ex. 1056); Arranz found “significant differences in

[progression-free survival] that favored the patients who received CVP + IFN” (Ex. 1067 at abstract); and Solal-Céligny reported that “the addition of IFN α to a doxorubicin-containing regimen for patients with advanced-stage and clinically aggressive FL [follicular lymphoma] not only increased PFS [progression-free survival], as in most other similar trials, but also prolonged OS [overall survival],” Ex. 1034 at abstract.

2. The German Low-Grade Lymphoma Study Group trial as reported in 1994 and 1996—CVP followed by interferon maintenance therapy

In 1994, Hiddemann published an introduction to an ongoing German study in which patients with LG-NHL were treated with CVP induction therapy followed by INF maintenance therapy. Ex. 1068. After reviewing the results of previous IFN maintenance therapy trials, Hiddemann concluded that better results were obtained when IFN maintenance therapy was continued for as long as possible. Specifically, Hiddemann noticed that the best results known at that time were from a French study (Ex. 1034) where IFN maintenance was continued for 18 months. As a result, Hiddemann hypothesized that the length of the disease free interval depends on the duration of IFN maintenance therapy—*i.e.*, the longer the maintenance therapy continued, the longer the disease free interval. The German study was therefore designed to continue interferon maintenance therapy for as long as possible, “until relapse or intolerable toxicity.” *Id.* at 35, col. 1. In 1996, Unterhalt

et. al. published a preliminary report from the same German study that stated that disease-free survival increased from 12 to 31 months in LG-NHL patients that were treated with IFN maintenance. Ex. 1006. Unterhalt is prior art under 35 U.S.C. §102(b).

C. Treating B-cell Lymphoma with Rituximab

Rituximab is a monoclonal antibody created by Idec Pharmaceuticals (now Biogen Idec). In 1997, rituximab was approved in the United States for the treatment of patients with relapsed or refractory low-grade or follicular, B-cell non-Hodgkin's lymphoma. It is marketed in the United States under the brand name RITUXAN®. Ex. 1008. Early in its development, rituximab was also known as "IDEC-C2B8." Ex. 1001 at col. 2, lines 59-60.

Rituximab is a humanized monoclonal antibody that binds to CD20, a protein specifically expressed on the surface of B-cells. Ex. 1008. Monoclonal antibodies are proteins that bind to a specific antigen, such as CD20. A humanized monoclonal antibody is a chimeric protein in which the antigen-binding regions from a mouse monoclonal antibody are fused into a human antibody backbone. Humanized antibodies can activate the human immune system when they bind to their target antigen, and they are less likely than murine antibodies to be rejected as a foreign protein by the immune system of a human patient. Thus, rituximab binds to a protein that is only expressed on B-cells, including the cancerous B-cells of

LG-NHL, and it activates the patient's immune system to kill the B-cells. Ex. 1002 at ¶¶ 74-75.

1. 1994 Maloney et al. Publication

In 1994, Maloney et al. published a paper titled, "Phase I Clinical Trial Using Escalating Single-Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients with Recurrent B-Cell Lymphoma." Ex. 1046.

Maloney described a phase I clinical trial using rituximab to treat NHL. The publication reported "a dose-dependent, rapid and specific depletion of the B cells in all patients." Ex. 1046 at 2460, col 2. All patients completed the planned antibody infusion with minimal infusion-related toxicity. *Id.* at 2460. The paper hypothesized that "extension of these studies to patients with minimal residual disease [*e.g.*, CR or complete remission], using antibody alone or in combination with conventional therapies, may provide the greatest benefit." *Id.* at 2465. Thus, the concept of rituximab maintenance therapy was disclosed to the public almost three years before the '172 patent's priority date. Ex. 1002 at ¶ 77.

2. The July 1997 FDA Biological Response Modifiers Advisory Committee Hearing

On July 25, 1997, the FDA's Biological Response Modifiers Advisory Committee held a public hearing with representatives from Idec Pharmaceuticals, including the '172 patent's named inventor, Dr. Grillo-López. Dr. Grillo-López presented data in support of Idec Pharmaceuticals' then-pending application to

market rituximab for relapsed or refractory LG-NHL patients. Ex. 1002 at ¶¶ 82-83. The transcript of the hearing (Ex. 1007, “FDA Transcript”) states at page 7 that the hearing was an “Open Public Hearing.” Given the public nature of the hearing, it would have been publicized by the FDA prior to the hearing. Additionally, the FDA transcript was available from the FDA prior to the 102(b) date and remains available on FDA’s website. *Id.* at ¶ 82. Thus, this transcript is prior art under 35 U.S.C. §102(b).

Dr. Grillo-López explained the advantages of rituximab as a targeted treatment for LG-NHL:

[Use of rituximab results in] very selective B-cell depletion. Mean serum immunoglobulin levels remain within normal limits. There is no apparent increase in the incidence of infections, and there is no apparent or significant impairment of clinical immunity due to B-cell depletion that occurs in these patients.

Ex. 1007 at 33:18-34:4.

Dr. Grillo-López disclosed that two patients had already been successfully treated with three courses of rituximab, and nearly 50 patients had been treated with two courses. *Id.* at 111:20 – 112:6. Since the patients studied by Dr. Grillo-López and colleagues were relapsed and refractory, they would have had prior chemotherapy and other induction treatments. Ex. 1002 at ¶ 84.

The FDA panel also heard a statement by Dr. Wendy Harpham, a practicing physician, who recounted her personal experience of having been diagnosed with LG-NHL and successfully treated with repeated doses of rituximab. Ex. 1007 at 9-15. Dr. Harpham explained that rituximab had allowed her to have a good quality of life while avoiding the toxicity associated with repeated courses of cytotoxic chemotherapy. *Id.* at 12, 14.

Dr. Bernard Parker, from the FDA, discussed the pharmacokinetics of rituximab. He explained that, because tumor cells essentially function as a sink that extracts rituximab from a patient's blood serum, the higher the tumor burden (*i.e.*, the greater the number of malignant B cells) the less rituximab remains in the serum. *Id.* at 78-79. Dr. Grillo-López agreed that higher serum levels correlate to higher activity: "serum levels of circulating free antibody do correlate with response." *Id.* at 72:5-9. These pharmacokinetic properties suggested that rituximab would be more suitable as a maintenance therapy than as a first-line treatment because newly diagnosed patients typically have a high tumor burden that would sequester much of the rituximab and thereby reduce its effective serum concentration, whereas patients with minimal residual disease or a reduced tumor burden would sequester less rituximab and therefore have higher serum levels and a stronger response. Ex. 1002 at ¶¶ 88-90.

3. 1997 FDA-Approved RITUXAN® Product Insert

In 1997, the FDA approved RITUXAN®, the commercial formulation of rituximab, for the treatment of patients with relapsed or refractory low-grade B-cell non-Hodgkin's lymphoma. The FDA-approved product insert for rituximab, dated November 1997 ("FDA label"), constitutes prior art under 35 U.S.C. § 102(b). *See* Ex. 1008.

According to the FDA label, the recommended dosage for rituximab was "375 mg/m² given as an IV infusion once weekly for four doses (days 1, 8, 15 and 22)." *Id.* at 2, col. 1. The FDA label notes that "[a]dministration of RITUXAN resulted in a rapid and sustained depletion of circulating and issue-based B cells." *Id.* at 1, col. 1. In fact, "[a]mong the 166 patients in the pivotal study, circulating B-cells . . . were depleted within the first three doses with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients" and that "B-cell recovery began at approximately six months following completion of treatment. Median B-cell levels returned to normal by twelve months following completion of treatment." *Id.*

4. 1998 McLaughlin et al. Publication

On August 7, 1998, McLaughlin et al. published a paper titled "Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent

Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program.”⁵ Ex. 1009. The study was published in the Journal of Clinical Oncology, a prestigious journal that would have been followed closely by those of ordinary skill. Ex. 1002 at ¶ 95. Dr. Grillo-Lopez, the named inventor on the ’172 patent, is the second-named author on the McLaughlin publication. This publication is prior art under 35 U.S.C. § 102(b).

McLaughlin describes a clinical trial in which LG-NHL patients were first treated with chemotherapy (including necessarily CVP). Most of the patients had achieved a complete response (CR) or a partial response (PR); *i.e.*, they had responded to the chemotherapy. These patients were then subsequently administered the standard course of rituximab (*i.e.*, four weekly doses of 375mg/m²). Although the patients who received rituximab therapy had relapsed prior to its administration, they had lower tumor burdens at the time of their rituximab therapy. *Id.* Thus, these patients had lower tumor burdens just like patients who receive maintenance therapy following induction with chemotherapy.

⁵ McLaughlin was one of the constituent parts of the ’180 provisional application. As previously discussed, the challenged claim is not entitled to a priority date that is the filing date of the ’180 provisional application. The earliest priority date to which the challenged claim may be entitled is the filing date of the ’202 application—August 11, 1999.

McLaughlin also strongly encouraged use of rituximab as maintenance therapy, and suggested that 6 months would be an appropriate interval between courses of rituximab maintenance therapy. Ex. 1002 at ¶¶ 95-97. Specifically, McLaughlin reported that “[p]atients who had achieved a CR or PR with their last prior chemotherapy course had a nonsignificant but somewhat better response to the antibody than those who were resistant to chemotherapy (53% v. 36%, P=.06).” Ex. 1009 at 2827, col. 2. One of ordinary skill would have concluded from this statement that rituximab was more effective in patients with a lower tumor burden at the time of rituximab therapy, as would occur during maintenance therapy. Ex. 1002 at ¶ 95. Indeed, McLaughlin explicitly encourages the use of rituximab maintenance therapy in a CR (minimal residual disease or MRD) setting following chemotherapy induction when it states that “[w]ith its established efficacy in the setting of measurable disease, the use of this agent in a minimal or subclinical disease setting is a consideration.” Ex. 1009 at 2831, col. 2. Additionally, McLaughlin shows that “the median B-cell count declined with [rituximab] treatment, to undetectable levels after the first dose for the majority” and “recovery of B cells started between 6 and 9 months, with recovery to normal between 9 and 12 months.” *Id.* at 2829, col. 2. In other words, administration of rituximab maintained depletion of B-cells for 6 months. Ex. 1002 at ¶ 96.

Biogen Idec maintains a commercial website that provides information about RITUXAN®. Ex. 1048. Notably, Biogen Idec's RITUXAN® website acknowledges that McLaughlin provided the foundation for, and strongly encouraged, the use of rituximab maintenance therapy following CVP induction therapy to treat LG-NHL. *Id.* at 3. Specifically, Biogen Idec states on its website that "B-cell depletion observed in the McLaughlin trial *formed the basis* for the ECOG 1496 dosing strategy following first-line CVP induction in low-grade NHL." (emphasis added). *Id.* The ECOG 1496 trial, for which McLaughlin "formed the basis," was also directed to LG-NHL and describes the precise method of claim 1 of the '172 patent. Ex. 1003. The ECOG 1496 trial is discussed in greater detail below.

5. The ECOG 4494 and ECOG 1496 Clinical Trials

The Eastern Cooperative Oncology Group (ECOG) organized two clinical trials to test the efficacy of rituximab maintenance therapy in B-cell Lymphoma. The ECOG 4494 trial was activated on December 12, 1997, Ex. 1004, and the ECOG 1496 trial was activated on March 19, 1998, Ex. 1003. A copy of the ECOG website from May 19, 1998, announced to the public that protocols for both trials were "active" as of May 1998. Ex. 1022. The declaration of a protocol as "active" marked the beginning of the period when the ECOG could provide the protocol to member institutions. Ex. 1002 at ¶ 98. Importantly, it also marked the beginning of

when physicians at ECOG member institutions could: (i) freely discuss the protocol and distribute it to other physicians and patients; (ii) obtain informed consent from patients; and (iii) enroll patients as subjects in the clinical trial. *Id.*

ECOG is an organization of member institutions dedicated to clinical cancer research. As of May 1998, its membership included hundreds of institutions around the world. Ex. 1051. Protocols for the ECOG 1496 and ECOG 4494 trials (Exs. 1003 and 1004, respectively) were distributed to all members of the cooperative shortly after activation and before May 19, 1998, with no confidentiality restrictions. Ex. 1002 at ¶¶ 99-106. Those of ordinary skill in the art would have known that protocols for any ECOG trial, including the schema of the protocols (which schematically depict the methods used during the trial), could be readily obtained either from ECOG (for oncologists affiliated with an ECOG member institution) or through an ECOG-affiliated oncologist (for those oncologists who may not have been affiliated with an ECOG member institution). *Id.* Physicians also would have been able to readily obtain information about any ECOG trial, including the protocol schema used in the ECOG trial, from the PDQ database, which is operated by the National Cancer Institute. Ex. 1053. In sum, a person of ordinary skill in the art could have, by May 19, 1998, learned about the ECOG 1496 and ECOG 4494 clinical trials, *e.g.*, by simply searching the ECOG website for clinical trials pertaining to rituximab. In addition, the protocols for these trials,

and particularly their associated protocol schema, were available to any interested physician (including oncologists) by May 19, 1998. Ex. 1002 at ¶¶ 100-106, 112. Additionally, at least the protocol schema contained in ECOG 1496 and ECOG 4494 (Exs. 1003 and 1004) would have been disseminated to other interested physicians, including oncologists, on or shortly after the clinical trials' were activated and prior to the 102(b) date. *Id.* at ¶ 105. The published protocols (Exs. 1003 and 1004) for these trials are prior art under 35 U.S.C. § 102(b).

ECOG 1496 (Ex. 1003) discusses the treatment of patients with LG-NHL. It is the same protocol referenced in column 13, lines 8-16 of the '172 patent (Ex. 1001), and it includes all of the same steps and other features recited in claim 1 of the '172 patent. Ex. 1002 at ¶¶ 107-110. Specifically, LG-NHL patients received standard CVP induction therapy. Ex. 1003 at schema and at 6-7. Patients whose LG-NHL had not progressed following induction were randomized to either receive rituximab maintenance therapy or be observed. Those randomized to the rituximab maintenance therapy arm had therefore received both the CVP induction and rituximab maintenance therapy as recited in claim 1. *Id.* The results of the ECOG 1496 trial were published by Hochster in 2009. Ex. 1040.

The protocol for the ECOG 4494 trial (Ex. 1004) included intermediate grade NHL patients. Those patients received CHOP induction chemotherapy either alone or together with rituximab, followed by rituximab maintenance therapy. The

rituximab maintenance therapy was provided precisely as recited in claim 1 of the '172 patent—*i.e.*, four weekly administrations of rituximab at a dose of 375 mg/m² every 6 months for 2 years. Ex. 1004 at schema,11. The ECOG 4494 trial was also described by McNeil in a February 1998 article published in the Journal of the National Cancer Institute. Ex. 1005. Specifically, the article states that the intermediate-grade NHL patients who had received CHOP induction chemotherapy would also receive rituximab maintenance therapy every 6 months for 2 years. *Id.* at 266, col. 3. It was understood well prior to February 1998—the date that the NCI Journal article was published—that the recommended dose for a single course of rituximab was 375 mg/m² administered weekly for four weeks. Ex. 1002 at ¶ 111; *see* Ex. 1008.

IX. THE CHALLENGED CLAIM IS UNPATENTABLE

A. Claim 1 is anticipated by ECOG 1496

ECOG 1496 (Ex. 1003) discloses all of the elements recited in claim 1 of the '172 patent. Specifically, (A) patients had “low-grade Non-Hodgkin’s lymphoma” (*id.* at Title); (B) patients in Arm B received standard CVP induction therapy (*id.* at Schema); (C) patients whose LG-NHL had not progressed following induction were randomized to either rituximab maintenance therapy or observation (*id.* at 6); and (D) the rituximab maintenance therapy consisted of rituximab at “a dose of 375 mg/m² weekly x 4 every 6 months for a total of 2 years beginning 4 weeks

after last chemotherapy” (*id.* at 7). Therefore, claim 1 of the ’172 patent is unpatentable under 35 U.S.C. § 102(b) because it is anticipated by ECOG 1496, which was published and widely available more than one year before the priority date of the claim. Ex. 1002 at ¶¶ 99-106, 108-109, 123.

B. Claim 1 of the ’172 patent is obvious

1. Those of ordinary skill in the art were motivated to identify an effective and tolerable maintenance therapy for treating LG-NHL

The importance of prolonging remission in LG-NHL patients, and identifying an effective means of doing so, was widely acknowledged for many years before the priority date of the ’172 patent. Ex. 1002 at ¶ 64. Low-grade NHL could be readily driven into remission by combination chemotherapy. *Id.* at ¶ 56. CVP had become a preferred induction chemotherapy because it was powerful enough to substantially reduce the LG-NHL tumor burden in most patients but had fewer toxic side effects than, for example, CHOP. *Id.* at ¶¶ 41, 55. However, even the most aggressive induction therapy left behind residual malignant B-cells that would inevitably start growing again, leading to relapse. *Id.* at ¶ 57. Recurrent LG-NHL could be treated once again by chemotherapy, but this was undesirable because relapse was accompanied by the return of debilitating disease symptoms, increased susceptibility to infection and the toxic side-effects of chemotherapy.

Furthermore, each successive remission was usually shorter than the last one in a relentless cycle of remission and relapse, eventually leading to death. *Id.* at ¶ 56.

Oncologists had long used maintenance therapy to treat the residual disease remaining after chemotherapy had driven LG-NHL into a complete or partial remission, for example. Ex. 1002 at ¶¶ 62-64. After limited success with maintenance chemotherapy, clinical researchers began investigating biologic therapeutics like IFN to activate the immune system to treat cancer. *Id.* at ¶¶ 65-66. IFN had undesirable side effects, but IFN maintenance therapy proved to be effective at substantially prolonging disease-free survival and even overall survival in patients whose LG-NHL had been previously treated with CVP induction therapy. *See id.* at ¶ 66; *see also* Exs. 1006, 1033, 1034, 1055, 1056, and 1067. Thus, the concept of maintenance therapy for LG-NHL patients had been firmly established well before the priority and 102(b) dates of the '172 patent. Ex. 1002 at ¶¶ 119-120.

2. Rituximab was known to possess properties that would be beneficial for maintenance therapy

Through their experience with IFN and other treatments, oncologists had identified several properties that an ideal maintenance therapy should possess. Ex. 1002 at ¶¶ 70-72, 117-118. First, it must effectively control the residual disease. Second, it must be suitable for long-term administration to keep the cancer in remission for as long as possible. Third, it should operate through a different

mechanism than the chemotherapeutic drugs used for induction therapy to reduce the chances of developing drug resistant cancer cells. Fourth, it should be less toxic than IFN in order to improve the patient's quality of life during remission.

Rituximab was approved by the FDA as a front-line therapy for LG-NHL in 1997, prior to the 102(b) date. Ex. 1008. The clinical testing that had been done to support FDA approval showed that rituximab possessed all of the attributes of an ideal maintenance therapy. Ex. 1002 at ¶¶ 73-81. First, it effectively treated the underlying cause of LG-NHL by targeted killing of B-cells. Ex. 1046. Second, it was effective for long-term treatment as demonstrated, for example, by the successful treatment of patients with multiple courses of rituximab therapy. Ex. 1002 at ¶¶ 83-87. Third, rituximab operated through a different mechanism than CVP chemotherapy. Fourth, as demonstrated in various studies, rituximab had fewer toxic side effects than IFN. *See e.g.*, Ex. 1002 at ¶ 91; Ex. 1038.

Rituximab did not merely fit the profile for an effective maintenance drug; the prior art strongly suggested and encouraged that it be used as maintenance therapy to treat LG-NHL. Ex. 1002 at ¶¶ 116-117. As discussed in the prior art, rituximab is particularly effective to treat lower tumor burdens (such as exists in CR and PR following induction chemotherapy). *Id.* at ¶¶ 113-115. After the majority of tumor cells have been killed by CVP, rituximab can more effectively target the residual disease. *Id.* at ¶¶ 88-90, 95. McLaughlin's data, for example,

suggested that rituximab was more effective in patients with a lower tumor burden, Ex. 1009 at 2927, col.2 and Fig. 3, and multiple publications had explicitly encouraged the use of rituximab maintenance therapy to treat minimal residual disease. Ex. 1046 at 2465; Ex. 1038 at 3273, col. 2; Ex. 1009 at 2831, col. 2. As of August 11, 1999, rituximab was so obviously suitable for maintenance therapy that there were five ongoing clinical trials using rituximab maintenance for the treatment of NHL. Exs. 1040-1044; Ex. 1002 at ¶ 73.

Perhaps most telling, Dr. Grillo-López, the named inventor on the '172 patent, admitted in a recently published retrospective article that many of his colleagues were skeptical about his plans in the early 1990's to use rituximab as induction therapy combined with chemotherapy because they believed that *“antibodies have limited efficacy and should be used only after chemotherapy, to treat the remaining minimal residual disease.”* Ex. 1037 at 402, col. 1.

3. All the elements of claim 1 were known in the prior art, and one of ordinary skill in the art was motivated to combine them with a reasonable expectation of success

Every element of the '172 patent claim was known before the priority and 102(b) dates. Furthermore, those of ordinary skill in the art were motivated to combine these elements because efforts to improve upon then-existing maintenance therapies (such as interferon maintenance therapy) were extensive and

well publicized, and every element had been previously used in the treatment of LG-NHL.

The use of rituximab maintenance therapy to treat LG-NHL was obvious because, when compared to other lymphomas, LG-NHL frequently relapsed; the cancerous B-cells were slow-growing and more difficult to eliminate using conventional chemotherapy. Ex. 1002 at ¶ 120. Thus, those of ordinary skill in the art were already using chemotherapy, such as CVP, followed by various forms of maintenance therapy to treat LG-NHL, including interferon maintenance therapy. *See, e.g.*, Ex. 1006. Moreover, although interferon maintenance therapy provided therapeutic benefits, such as an increase in progression-free and overall survivals, those of ordinary skill sought out a less toxic alternative that could be administered over a longer period of time. Ex. 1002 at ¶¶ 66, 117. Rituximab was known to be less toxic than interferon and had already demonstrated its ability to deplete cancerous B-cells in LG-NHL. Ex. 1039. Accordingly, before the priority and 102(b) dates, those of ordinary skill in the art recognized rituximab's utility as a maintenance therapy and encouraged others to use it as such. *See* Ex. 1002 at ¶ 115; *see also, e.g.*, Ex. 1046 at 2465; Ex. 1038 at 3273, col. 2; Ex. 1009 at 2831, col. 2.

CVP was, and still is, the preferred induction chemotherapy for LG-NHL. Ex. 1002 at ¶ 55; Ex. 1011. It would have been obvious to use CVP, the induction

therapy most suitable for LG-NHL, rather than CHOP, a more potent but also more toxic combination that was preferred for more aggressive forms of NHL. Ex. 1002 at ¶ 121. Rituximab maintenance therapy after CHOP induction therapy for the treatment of intermediate-grade or high-grade NHL was known in the prior art. Exs. 1004-1005. It would have been obvious to modify this protocol by using CVP instead of CHOP to treat LG-NHL. Ex. 1002 at ¶ 124.

The claimed rituximab dosage of four weekly administrations at 375 mg/m² had been used in multiple clinical trials and was the recommended dosage for treating LG-NHL, as provided in RITUXAN's® 1997 FDA-approved label. Ex. 1008. Thus, it would have been obvious to continue using the same dosage of the same drug to treat the same disease. Ex. 1002 at ¶ 93.

Administering rituximab maintenance therapy every six months for two years was exactly the same schedule described in ECOG 4494 (Ex. 1004) and McNeil (Ex. 1005), both of which describe rituximab maintenance therapy for more aggressive NHL. Even without these prior art references, the schedule would have been obvious because, for example, B-cell depletion after rituximab therapy was known to last for six months (Exs. 1009, 1002 at ¶ 118), experience with IFN maintenance had shown that maintenance therapy for LG-NHL was more effective when it was continued for as long as possible (Ex. 1068), and NHL patients had already been successfully treated with multiple courses of rituximab (Exs. 1007,

1002 at ¶¶ 92-94). Hainsworth independently devised an identical rituximab maintenance protocol, providing further confirmation that that the protocol was obvious. Ex. 1043 at 1612, col. 1.

Additionally, one of ordinary skill in the art would have had at least a reasonable expectation of success in combining all the known prior art elements to arrive at the claimed subject matter. Ex. 1002 at ¶¶ 113-121. CVP induction therapy followed by interferon maintenance therapy had already been shown to be effective for the treatment of LG-NHL. Ex. 1009. Replacing interferon maintenance therapy with rituximab maintenance therapy would have been reasonably expected to be successful given, among other reasons, rituximab's known lower toxicity profile (Exs. 1046 and 1038), its proven effectiveness in treating LG-NHL (Exs. 1038 and 1009), and that it had been effectively administered multiple times to numerous patients (Ex. 1007).

C. Proposed Combinations of Prior Art That Anticipate and Render Obvious Claim 1 of the '172 Patent

1. ECOG 1496 (Ex. 1003) Anticipates Claim 1

As described in section IX.A, ECOG 1496 describes the precise method of claim 1. Therefore, ECOG 1496 anticipates claim 1. Ex. 1002 at ¶ 123.

2. ECOG 4494 (Ex. 1004) Renders Obvious Claim 1

ECOG 4494 discloses the rituximab maintenance therapy method claimed in the '172 patent, "4 weekly doses repeated every 6 mos x 2 years", but it treats

intermediate-grade NHL instead of LG-NHL and uses CHOP instead of CVP for induction. Oncologists would have been motivated to use the rituximab maintenance therapy method of ECOG 4494 to treat LG-NHL because, for example, Maloney (Ex. 1046 at 2465; Ex. 1038 at 3273, col. 2); McLaughlin (Ex. 1009 at 2831, col. 2), and others had encouraged the use of rituximab maintenance therapy to treat the residual disease remaining after chemotherapy in LG-NHL patients. Ex. 1002 at ¶ 124. In addition, interferon maintenance therapy had been used in conjunction with CVP induction therapy to treat LG-NHL. Ex. 1006. Thus, one of ordinary skill in the art knew that maintenance therapy was an effective way to treat LG-NHL. Ex. 1002 at ¶ 125. Additionally, interferon maintenance therapy was tested in more aggressive NHL before LG-NHL trials were conducted, so there was precedent for adapting more aggressive NHL therapies for the treatment of LG-NHL. Exs. 1055-56, 1002 at ¶ 120. Furthermore, those of ordinary skill would have been motivated to substitute CVP for the CHOP used in ECOG 4494 because CVP had lower toxicity and was therefore a standard induction therapy for LG-NHL. Ex. 1011.

Since interferon had been successfully administered as maintenance therapy for LG-NHL, those of ordinary skill would have reasonably expected similar success with rituximab maintenance therapy, particularly in view of the fact that rituximab was known to have lower toxicity than interferon. Ex. 1002 at ¶ 73. Both

were known to be effective against LG-NHL, and to be immune response modifiers with a mechanism that is complementary to the mechanisms of chemotherapy drugs, including CVP. Ex. 1002 at ¶ 65.

Indeed, consistent with the conclusion that ECOG 4494 renders the '172 patent claim obvious is the notable fact that the ECOG 4494 and ECOG 1496 trials, which became active only a few months apart, used the exact same rituximab maintenance therapy dosing and schedule, despite having completely different people leading the trials, and that Hainsworth independently devised the identical rituximab maintenance protocol. *Ecolochem v S. Cal. Edison* 227 F.3d 1361, 1379 (Fed. Cir. 2000) (“The fact of near-simultaneous invention, though not determinative of statutory obviousness, is strong evidence of what constitutes the level of ordinary skill in the art.”); *see also* Ex. 1002 at ¶¶ 94,126.

3. ECOG 4494 (Ex. 1004) In Combination with Unterhalt 1996 (Ex. 1006) Renders Obvious Claim 1

Claim 1 is rendered obvious for all the same reasons discussed above in connection with ECOG 4494 alone, and for the additional reason that it further would have been obvious to modify the method discussed in ECOG 4494 to get the method of claim 1 given the teachings in Unterhalt. Ex. 1002 at ¶ 127. Specifically, Unterhalt successfully treated LG-NHL with CVP induction therapy followed by interferon maintenance therapy. Rituximab and interferon are both immune response modifiers with a mechanism that is complementary to the mechanisms of

chemotherapy drugs, including CVP. Rituximab, however, was known to have lower toxicity than interferon. Hence, Unterhalt provides further motivation to apply the rituximab maintenance therapy of ECOG 4494 to the treatment of LG-NHL after CVP induction therapy.

One of ordinary skill would have been motivated to modify ECOG 4494 (Ex. 1004) with what was discussed in Unterhalt (Ex. 1006) and would have reasonably expected to succeed in obtaining claim 1 of the '172 patent in view of, for example: (i) the fact that both address NHL; (ii) other maintenance therapies for the treatment of LG-NHL had first been done in higher grades of NHL; (iii) CHOP had previously been used as induction therapy in LG-NHL; (iv) others had encouraged the use of rituximab maintenance therapy following chemotherapeutic induction therapy to treat LG-NHL; and (v) Unterhalt had treated LG-NHL using CVP induction therapy followed by BRM maintenance therapy and demonstrated a “significant prolongation of DFS [disease-free survival].” Ex. 1002 at ¶ 127.

4. ECOG 4494 (Ex. 1004) In Combination with the FDA Transcript (Ex. 1007) Renders Obvious Claim 1

Claim 1 is rendered obvious for all the same reasons discussed above in connection with ECOG 4494 alone, and for the additional reason that it further would have been obvious to modify the method discussed in ECOG 4494 to obtain the method of claim 1 of the '172 patent given the discussion in the 1997 FDA Transcript. Ex. 1002 at ¶ 128. Specifically, the 1997 FDA Transcript discusses

treating LG-NHL with multiple courses of rituximab therapy, and describes at least one patient whose follicular LG-NHL was treated with CVP, which resulted in a CR of 11 months, followed by multiple courses of rituximab, each of which resulted in a PR lasting 20 months or more.

One of ordinary skill would have been motivated to modify the protocol of ECOG 4494 with what was discussed in the FDA Transcript and would have reasonably expected to succeed in obtaining claim 1 of the '172 patent in view of, for example, the fact that both address NHL, other maintenance therapies for the treatment of LG-NHL had first been done in higher grades of NHL, CHOP had previously been used as induction therapy in LG-NHL, others had encouraged the use of rituximab maintenance therapy following chemotherapeutic induction therapy to treat LG-NHL, and the 1997 FDA Transcript encouraged the use of multiple courses of rituximab following CVP therapy to treat LG-NHL and discussed the benefits of using rituximab when tumor burden was reduced (*e.g.*, following CVP induction therapy). Ex. 1002 at ¶ 128.

5. McNeil (Ex. 1005) Renders Obvious Claim 1

As discussed above, McNeil reports on the ECOG 4494 trial. Like ECOG 4494, it discloses the use of CHOP induction therapy followed by rituximab maintenance therapy to treat intermediate-grade NHL. Further, like ECOG 4494, it also discloses that rituximab maintenance therapy is given every 6 months for two

years. Ex. 1005 at 266, col. 3. A person of ordinary skill in the art reading McNeil would understand that each course of the rituximab maintenance therapy to which the article is referring is the standard rituximab dosing regimen of four weekly doses of 375mg/m². Ex. 1002 at ¶ 129. Indeed, that is the precise regimen described in the 1997 FDA Label (Ex. 1008). For the same reasons discussed in connection with ECOG 4494, it would have been obvious to those of ordinary skill to use the protocol described in McNeil to treat LG-NHL, and it further would have been obvious to do so using standard CVP induction therapy, instead of CHOP, to treat LG-NHL.

6. McNeil (Ex. 1005) In Combination with the 1997 Rituxan® Label (Ex. 1008) Renders Obvious Claim 1

As discussed above, claim 1 is rendered obvious by McNeil. Claim 1 is further rendered obvious by the 1997 Rituxan® Label, which makes explicit what oncologists would understand from McNeil—namely, that each course of rituximab therapy is the standard rituximab dosing regimen of 4 weekly doses of 375mg/m². Ex. 1002 at ¶ 130. One of ordinary skill would have been motivated to modify McNeil with what was discussed in the 1997 Rituxan® Label and would have reasonably expected to succeed in obtaining claim 1 of the '172 patent in view of, for example, the fact that the 1997 Rituxan® Label disclosed the FDA-approved standard dosing regimen of rituximab for the treatment of LG-NHL.

7. Either McNeil (Ex. 1005) Alone (or McNeil In Combination With the 1997 Rituxan® Label (Ex. 1008)) In Combination With Unterhalt (Ex. 1006) Renders Obvious Claim 1

As discussed above, both McNeil alone and McNeil in combination with the 1997 Rituxan® Label render obvious claim 1. As discussed in section 3 above with respect to ECOG 4494, claim 1 is further rendered obvious by Unterhalt, which discusses successfully treating LG-NHL with CVP induction therapy followed by IFN maintenance therapy. *See also* Ex. 1002 at ¶ 131. Unterhalt emphasizes what would have been apparent to one of ordinary skill from McNeil—specifically, that the method described in McNeil could be used for the treatment of LG-NHL and that CVP induction therapy could be used instead of CHOP induction therapy.

One of ordinary skill would have been motivated to modify McNeil with what was discussed in Unterhalt and would have reasonably expected to succeed in arriving at claim 1 of the '172 patent in view of, for example, the fact that both address NHL, other maintenance therapies for the treatment of LG-NHL had first been done in higher grades of NHL, CHOP had previously been used as induction therapy in LG-NHL, others had encouraged the use of rituximab maintenance therapy following chemotherapeutic induction therapy to treat LG-NHL, and Unterhalt had treated LG-NHL using CVP induction therapy followed by BRM maintenance therapy and demonstrated a “significant prolongation of DFS [disease-free survival].” Ex. 1002 at ¶ 131.

8. McNeil (Ex. 1005) Alone (or McNeil In Combination with the 1997 Rituxan® Label (Ex. 1008)) In Combination With the 1997 FDA Transcript (Ex. 1007) Renders Obvious Claim 1

As discussed above, both McNeil alone and McNeil in combination with the 1997 Rituxan® Label render obvious claim 1. Claim 1 is further rendered obvious by the 1997 FDA Transcript, which discusses the use of CVP to treat a form of LG-NHL, followed by multiple courses of rituximab therapy. Ex. 1002 at ¶ 132.

One of ordinary skill would have been motivated to modify McNeil with what was discussed in the 1997 FDA Transcript and would have reasonably expected to succeed in obtaining claim 1 of the '172 patent in view of, for example, the fact that both address NHL, other maintenance therapies for the treatment of LG-NHL had first been done in higher grades of NHL, CHOP had previously been used as induction therapy in LG-NHL, others had encouraged the use of rituximab maintenance therapy following chemotherapeutic induction therapy to treat LG-NHL, and the 1997 FDA Transcript encouraged the use of multiple courses of rituximab following CVP therapy to treat LG-NHL and discussed the benefits of using rituximab when tumor burden was reduced (*e.g.*, following CVP induction therapy). Ex. 1002 at ¶ 132.

9. McLaughlin (Ex. 1009) Renders Obvious Claim 1

McLaughlin describes a clinical trial in which LG-NHL patients were first treated with chemotherapy, including necessarily CVP, and subsequently treated

with 375mg/m² rituximab, administered once weekly for a total of four infusions. Ex. 1002 at ¶ 133.

As stated on Biogen Idec's RITUXAN® website, the "B-cell depletion observed in McLaughlin *formed the basis* for the ECOG 1496 dosing strategy following first-line CVP induction in low-grade NHL." (emphasis added). Ex. 1048. As discussed above, the ECOG 1496 trial tested the precise method claimed in claim 1 of the '172 patent. Thus, this statement by the patent owner, Biogen Idec, is a concession that claim 1 is obvious over McLaughlin. Ex. 1002 at ¶ 135.

Although the LG-NHL of the patients in the McLaughlin study had relapsed following chemotherapy, the patients had lower tumor burdens at the time of rituximab administration. Ex. 1002 at ¶ 95. Indeed, McLaughlin acknowledged that rituximab produced a better response in patients who had experienced a CR or PR following chemotherapy. Ex. 1009 at 2827. One of ordinary skill would have understood from this that rituximab was more effective when patients had lower tumor burdens following chemotherapy, which is precisely the case when rituximab maintenance therapy is administered. Ex. 1002 at ¶¶ 95, 133. These results caused McLaughlin to strongly encourage using rituximab in a maintenance therapy setting. *Id.* at 2831. Upon reading McLaughlin, one of ordinary skill in the art would have been encouraged to use rituximab as maintenance therapy for the treatment of LG-NHL. Ex. 1002 at ¶¶ 133-134.

CVP chemotherapy for LG-NHL would have been a logical choice as an induction therapy to use with rituximab maintenance therapy, particularly given that CVP induction therapy had previously been used to treat LG-NHL. Indeed, at least some of the patients treated in McLaughlin necessarily had been treated with CVP to achieve a CR or PR because CVP was the preferred combination chemotherapy to treat LG-NHL. Ex. 1011; Ex. 1002 at ¶ 133.

Those of ordinary skill reading McLaughlin also would have been motivated to administer multiple courses of rituximab maintenance therapy in order to prolong the period of remission for as long as possible. Ex. 1002 at ¶ 133. The length of treatment in trials using maintenance therapy drugs, such as interferon, was limited due to concerns regarding toxicity. In contrast, McLaughlin stated that “[t]he toxicity of the current program was notably mild, particularly with respect to myelosuppressive toxicities that are typical of standard chemotherapy or RIT [radioimmunotherapy]. Adverse events occurred mainly with the first infusion...By the second and subsequent infusions, the majority of patients experienced no further infusion-related toxicities.” Ex. 1009 at 2831-31. Accordingly, it would have been obvious to one of ordinary skill to administer as many courses of rituximab maintenance therapy as possible to prolong the period of remission for as long as possible and, by doing so, to provide maintenance therapy for 2 years, or even longer.

Moreover, one of ordinary skill would have understood from McLaughlin that the courses of rituximab maintenance therapy should be separated by 6 months given that administration of a course of rituximab resulted in rapid depletion of B-cells and recovery of the B-cells did not occur until 6 months later. *Id.* at 2829 and Figure 3.

Given it was known that CVP induction therapy followed by maintenance therapy using interferon had successfully treated LG-NHL, and that rituximab had a mild toxicity profile, one of ordinary skill would have reasonably expected to successfully use rituximab maintenance therapy following CVP induction therapy to treat LG-NHL as encouraged by McLaughlin 1998. Ex. 1002 at ¶¶ 133-135.

10. McLaughlin 1998 (Ex. 1009) In Combination with McNeil (Ex. 1005) Renders Obvious Claim 1

As discussed above, McLaughlin renders obvious claim 1 of the '172 patent. Claim 1 is further rendered obvious by McNeil, which discusses the treatment of intermediate-grade NHL by using CHOP induction therapy, followed by rituximab maintenance therapy every 6 months to provide maintenance therapy for two years. Ex. 1002 at ¶ 136. Given, for example, the strong encouragement in McLaughlin to use rituximab maintenance therapy in a LG-NHL setting, one of ordinary skill would have viewed the rituximab maintenance therapy regimen discussed in McNeil as a logical choice. This particularly would have been the case given that the CHOP induction therapy used in McNeil had previously been used to treat LG-

NHL (Ex. 1023 at 62), the maintenance therapy discussed in McNeil was consistent with the observation in McLaughlin that use of rituximab to treat LG-NHL resulted in B cell depletion that lasted at least 6 months (Ex. 1009 at 2829 and Figure 3), and maintenance therapies for the treatment of LG-NHL had previously been considered first in the context of treating higher grades of NHL, such as intermediate-grade NHL (Exs. 1055-6). Moreover, standard CVP chemotherapy for LG-NHL would have been a logical choice as induction therapy for use with rituximab maintenance therapy. Ex. 1011; Ex. 1002 at ¶ 133. In any event, at least some of the patients treated in McLaughlin were necessarily treated with CVP to achieve a CR or PR prior to administration of rituximab. Ex. 1002 at ¶ 133.

D. Claim Chart Comparing the Challenged Claim to the Prior Art

Comparison to Claim 1 of U.S. Patent No. 8,329,172	
Claim element	Exemplary Disclosure in Prior Art
A method of treating low grade B-cell non-Hodgkin's lymphoma in a human patient comprising	ECOG 1496, CVP with Rituximab maintenance, 1998 (Ex. 1003) <ul style="list-style-type: none"> • “Patients must have Stage III-IV (Ann Arbor classification) low-grade Non-Hodgkin’s lymphoma” (p. 3) ECOG 4494, CHOP with Rituximab maintenance, 1997 (Ex. 1004) <ul style="list-style-type: none"> • “All patients must have a tissue diagnosis of non-Hodgkin’s lymphoma, intermediate or high-grade histology ...” (p. 5)

Comparison to Claim 1 of U.S. Patent No. 8,329,172

Claim element	Exemplary Disclosure in Prior Art
	<p>Unterhalt, Interferon maintenance, 1996 (Ex. 1006)</p> <ul style="list-style-type: none"> • “[P]atients with advanced stage III and IV follicle center lymphoma and mantle cell lymphoma” <p>FDA Transcript, Biological Response Modifiers Advisory Committee, 1997 (Ex. 1007)</p> <ul style="list-style-type: none"> • "I [Dr. Wendy Harpham] am a... seven-year survivor of small cleaved cell follicular non-Hodgkin's lymphoma." (p. 9:13-16) • “This patient was a 30-years old white male with follicular, small cleaved lymphoma diagnosed in '90.” (p. 125:13-14) <p>McNeil, NCI Journal, Feb. 1998 (Ex. 1005)</p> <ul style="list-style-type: none"> • “Researchers in December launched a new randomized trial for elderly patients with intermediate-grade non-Hodgkin 's lymphoma (NHL)” (p. 266, col 1) <p>1997 Rituxan® Label (Ex. 1008)</p> <ul style="list-style-type: none"> • “RITUXAN is indicated for the treatment of patients with relapsed or refractory low-grade or follicular CD20 positive B-cell non-Hodgkin’s lymphoma.” (p. 1, col. 2) <p>McLaughlin, Rituximab for Indolent Lymphoma, 1998 (Ex. 1009)</p> <ul style="list-style-type: none"> • “Adult patients with relapsed low grade or follicular B-cell lymphoma” (p. 2826, col. 1)
<p>administering to the patient chemotherapy consisting of CVP therapy to which the patient responds,</p>	<p>ECOG 1496, CVP with Rituximab maintenance, 1998 (Ex. 1003)</p> <ul style="list-style-type: none"> • “Patients randomized to this arm (standard therapy) will receive cyclophosphamide 1000 mg/m² (maximum 200 mg, administer in 500 cc D5W over 30 – 45 minutes), vincristine 1.4 mg/m² (maximum

Comparison to Claim 1 of U.S. Patent No. 8,329,172

Claim element	Exemplary Disclosure in Prior Art
	<p>2.0 mg, IV push through running IV) day 1 and prednisone 100 mg/m² orally days 1-5. Cycles will be repeated q21 days.” (p. 7)</p> <ul style="list-style-type: none"> • “Those completing the induction phase without frank progression ...” (p. 6) <p>ECOG 4494, CHOP with Rituximab maintenance, 1997 (Ex. 1004)</p> <ul style="list-style-type: none"> • “Arm B – CHOP (p. 10)” • “Patients who are in complete remission by restaging after both four and six cycles of therapy ...” (Schema) <p>Unterhalt, Interferon maintenance, 1996 (Ex. 1006)</p> <ul style="list-style-type: none"> • “responding to an initial cytoreductive therapy with a combination of Cyclophosphamide, Vincristine, Prednisone (COP)” <p>FDA Transcript, Biological Response Modifiers Advisory Committee, 1997 (Ex. 1007)</p> <ul style="list-style-type: none"> • “He initially received chemotherapy with a CVP regimen, and had only a partial response lasting for 10 months. Upon progression of disease, he was treated with ABMT with cytoxan VP 16 and total body irradiation, and had a complete response which lasted for 18 months. He progressed and was treated with CVP, had a CR lasting 11 months.” (p. 125:14-20) <p>McNeil, NCI Journal, Feb. 1998 (Ex. 1005)</p> <ul style="list-style-type: none"> • “[P]atients who responded [to CHOP]....” (p. 266, col 3) • “CHOP alternatives could also turn out [to] be less toxic chemotherapy regimens, another area where several NHL studies are underway in the elderly. One reason for poorer outcomes in older patients is thought to be that CHOP, like some other chemotherapy regimens, is more toxic in this age group.” (p. 266, col 3)

Comparison to Claim 1 of U.S. Patent No. 8,329,172

Claim element	Exemplary Disclosure in Prior Art
	<p>McLaughlin, Rituximab for Indolent Lymphoma, 1998 (Ex. 1009)</p> <ul style="list-style-type: none"> • “Prior therapy included chemotherapy in 97%, ...” (p. 2826, col. 2) • “166 patients were enrolled”, “Twenty-two patients had been resistant to all prior chemotherapy (had never achieved a CR or PR), while 45 were resistant to their most recent chemotherapy before study entry.” (p. 2826, col. 2)
<p>followed by rituximab maintenance therapy,</p>	<p>ECOG 1496, CVP with Rituximab maintenance, 1998 (Ex. 1003)</p> <ul style="list-style-type: none"> • “Those completing the induction phase without frank progression will be randomized in Step 2 to maintenance therapy with anti-CD20 vs. observation.” (p. 6) • “Following induction chemotherapy as above, patients will be randomized to maintenance therapy with anti-CD20 vs. observation.” (p. 10) <p>ECOG 4494, CHOP with Rituximab maintenance, 1997 (Ex. 1004)</p> <ul style="list-style-type: none"> • “Patients who are in complete remission by restaging after both four and six cycles of therapy will then be randomized to either anti-CD20 maintenance (Arm C) or to observation (Arm D).” (Schema) <p>Unterhalt, Interferon maintenance, 1996 (Ex. 1006)</p> <ul style="list-style-type: none"> • “IFN-α maintenance” <p>FDA Transcript, Biological Response Modifiers Advisory Committee, 1997 (Ex. 1007)</p> <ul style="list-style-type: none"> • “He initially received chemotherapy with a CVP regimen, and had only a partial response lasting for 10 months. Upon progression of disease, he was treated with ABMT with cytoxan VP 16 and total body irradiation, and had a complete response which lasted

Comparison to Claim 1 of U.S. Patent No. 8,329,172

Claim element	Exemplary Disclosure in Prior Art
	<p>for 18 months. He progressed and was treated with CVP, had a CR lasting 11 months.” (p. 125:14-20)</p> <ul style="list-style-type: none"> • “Following this, he had progression of disease and was treated with IDEC-C2B8 back in December of '93. This patient had a very good partial response.” (p. 125:21-24) • “Upon progression of disease, this patient who was wiser than we were, insisted that he get the antibody again.” (p. 127:4-6) <p>McNeil, NCI Journal, Feb. 1998 (Ex. 1005)</p> <ul style="list-style-type: none"> • “After initial therapy, patients who responded will be again randomly assigned to receive the maintenance regimen – Rituxan” (p. 266, col 3) <p>McLaughlin, Rituximab for Indolent Lymphoma, 1998 (Ex. 1009)</p> <ul style="list-style-type: none"> • “Prior therapy included chemotherapy in 97%, ...” (p. 2826, col. 2) • “166 patients were enrolled”, “Twenty-two patients had been resistant to all prior chemotherapy (had never achieved a CR or PR), while 45 were resistant to their most recent chemotherapy before study entry.” (p. 2826, col. 2) • “[Patients] had to be at least 3 weeks beyond prior standard therapy including corticosteroids,” (p. 2826, col. 1) • “The current report summarizes results of a multiinstitutional trial of a four-dose course of therapy with this chimeric anti-CD20 monoclonal antibody.” (p. 2826, col. 1) • “Patients who had achieved a CR or PR with their last prior chemotherapy course had a nonsignificant but somewhat better response to the antibody than those who were resistant to chemotherapy (53% v 36%, P = .06).” (p. 2827, col. 2)

Comparison to Claim 1 of U.S. Patent No. 8,329,172

Claim element	Exemplary Disclosure in Prior Art
	<ul style="list-style-type: none"> • “[w]ith its established efficacy in the setting of measurable disease, the use of this agent [rituximab] in a minimal or subclinical disease setting is a consideration.” (p. 2831, col. 2)
<p>wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m² every 6 months, and wherein the maintenance therapy is provided for 2 years.</p>	<p>ECOG 1496, CVP with Rituximab maintenance, 1998 (Ex. 1003)</p> <ul style="list-style-type: none"> • “Anti-CD20 will be given at a dose of 375 mg/m² weekly x 4 every 6 months for a total of 2 years beginning 4 weeks after last chemotherapy.” (Schema and p. 10) <p>ECOG 4494, CHOP with Rituximab maintenance, 1997 (Ex. 1004)</p> <ul style="list-style-type: none"> • “Anti-CD20 Maintenance: 4 weekly doses repeated every 6 mos x 2 years” (Schema) • “A cycle of maintenance therapy will consist of IDEC-C2B8, 375 mg/m² IV, given weekly for four consecutive weeks, if the maintenance week one IgG level is >500 mg/dl. This four-week cycle of therapy will be administered at six-month intervals for a total of four cycles. If the IgG level is ≤500 mg/dl for any given cycle of maintenance therapy, the IgG level should be followed monthly and further maintenance therapy withheld until the IgG level is > 500 mg/dl.” (p. 11) <p>Unterhalt, Interferon maintenance, 1996 (Ex. 1006)</p> <ul style="list-style-type: none"> • “IFN-α was given without a fixed time limitation until relapse or intolerable [sic] toxicity” <p>FDA Transcript, Biological Response Modifiers Advisory Committee, 1997 (Ex. 1007)</p> <ul style="list-style-type: none"> • “Treatment is well tolerated, and retreatment is feasible, and in fact, we have retreated 22 patients who received treatment twice, and 2 patients who have received treatment three times.” (p. 35:8-11)

Comparison to Claim 1 of U.S. Patent No. 8,329,172

Claim element	Exemplary Disclosure in Prior Art
	<ul style="list-style-type: none"> • “As far as I know, I [Wendy Harpham], am the first person ever to receive the IDEC Mab three times.” (p. 12:15-17) • “Each of the last two courses of C2B8 brought me eight months with minimal toxicity. Repeated courses appear to be at least as effective for me as my first courses.” (p. 13: 5-8) • “Upon progression of disease, this patient who was wiser than we were, insisted that he get the antibody again.” (p. 127:4-6) <p>McNeil, NCI Journal, Feb. 1998 (Ex. 1005)</p> <ul style="list-style-type: none"> • “Rituxan every 6 months for 2 years - or observation” (p. 266, col 3) <p>1997 Rituxan® Label (Ex. 1008)</p> <ul style="list-style-type: none"> • “The recommended dosage of RITUXAN is 375 mg/m² given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22).” (p. 2, col. 1) • “Administration of RITUXAN resulted in a rapid and sustained depletion of circulating and tissue-based B cell ... Among the 166 patients in the pivotal study, circulating B-cells (measured as CD19+ cells) were depleted within the first three doses with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients. ... B-cell recovery began at approximately six months following completion of treatment.” (p. 2, col. 1) <p>McLaughlin, Rituximab for Indolent Lymphoma, 1998 (Ex. 1009)</p> <ul style="list-style-type: none"> • “The antibody dose was 375 mg/m², administered intravenously once weekly for a total of four infusions (days 1, 8, 15, and 22) on an outpatient basis.” (p. 2826, col. 1)

Comparison to Claim 1 of U.S. Patent No. 8,329,172	
Claim element	Exemplary Disclosure in Prior Art
	<ul style="list-style-type: none"> • Fig 3. • “the median B-cell count declined with treatment, to undetectable levels after the first dose for the majority ... Recovery of B cells started between 6 and 9 months, with recovery to normal between 9 and 12 months.” (p. 2829, col. 2) • “[t]he toxicity of the current program was notably mild, particularly with respect to myelosuppressive toxicities that are typical of standard chemotherapy or RIT. Adverse events occurred mainly with the first infusion...By the second and subsequent infusions, the majority of patients experienced no further infusion-related toxicities.” (pp. 2830-31)

X. HOCHSTER FAILS TO ESTABLISH UNEXPECTED RESULTS

As an initial matter, “where a claimed invention represents no more than the predictable use of prior art elements according to established functions . . . evidence of secondary indicia are frequently deemed inadequate to establish non-obviousness.” *Ohio Willow Wood Co. v. Alps S., LLC*, 735 F.3d 1333, 1344 (Fed. Cir. 2013). “Weak secondary considerations generally do not overcome a strong prima facie case of obviousness.” *Western Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1373 (Fed. Cir. 2010); *Hoffman La Roche, Inc. v. Apotex, Inc.*, 748 F.3d 1326, 1334-35 (Fed. Cir. 2014) (finding that evidence of secondary considerations did not rebut *prima facie* showing of obviousness).

Claim 1 was ultimately allowed “in view of applicants’ arguments regarding unexpected results.” Ex. 1069 at 2. Relying on Hochster, which was published 10 years after the priority date of the challenged claim, applicants argued that the claimed method produced unexpected results, specifically “prolongation of PFS [progression free survival] for MR-treated [maintenance rituximab] patients with a median more than three times longer (4.3 v. 1.3 years) and a 60% reduction in progression risk (HR = 0.4; P < 10⁻⁹.)” Ex. 1064 at 7. To the contrary, the prolonged progression-free survival reported by Hochster was entirely expected. Ex. 1002 at ¶¶ 119, 137-140.

First, Hochster itself emphasized that prolonged remission was expected when it concluded that “[o]ur study *confirmed the hypothesis* that rituximab would be an effective and safe maintenance after CVP chemotherapy.” (emphasis added). Ex. 1040 at 1611, col. 1.

Furthermore, the applicant’s unexpected results argument was limited to demonstrating that CVP induction followed by rituximab maintenance achieves unexpected results compared to *CVP induction alone*. Ex. 1002 at ¶ 139. Applicant did not argue that the claimed method achieves unexpected results when compared to CVP induction *followed by other forms of maintenance therapy* that had been used to treat LG-NHL, e.g., IFN maintenance therapy. (emphasis added). See Ex. 1064 at 7-8.

Indeed, multiple studies published before the 102(b) date of the '172 patent described successfully treating LG-NHL with IFN maintenance therapy to enhance progression free survival and overall survival. For example, Unterhalt treated LG-NHL with CVP followed by IFN maintenance and concluded that “these data clearly demonstrate a prolonged effect of IFN- α maintenance in low grade lymphoma which provides a significant prolongation of DFS [disease free survival] and the interval without the requirement of further cytostatic therapy in patients with advanced low grade NHL.” Ex. 1002 at ¶ 140. Similarly, Aviles reported that “with a median follow-up of 11 years (March 1997), disease progression has been observed in only 40% of our patients who received IFN maintenance therapy [for LG-NHL], compared to 93% in the control group [no IFN maintenance therapy]. Overall survival was statistically significantly different between groups at 11 years of follow-up: 60% of the patients who received IFN were alive compared to only 31% in the control group ($p < 0.001$).” Ex. 1033 at 155, col. 1. Furthermore, Solal-Celigny stated that “these results confirm that the addition of IFN α to a doxorubicin-containing regimen for patients with advanced-stage and clinically aggressive FL [low grade follicular lymphoma] not only increased PFS [progression-free survival], as in most other similar trials, but also prolonged OS [overall survival].” Ex. 1034 at abstract.

Even Hochster, after citing four studies that tested interferon maintenance for the treatment of LG-NHL, candidly acknowledged that rituximab maintenance was also expected to prolong progression-free survival, stating that “[t]hese experiences with continuation or maintenance therapy [with interferon] *suggested*, however, that an active biologic agent with a favorable safety profile and high patient acceptability [rituximab] would improve clinical outcome in indolent lymphoma.” (emphasis added). Ex. 1040 at 1607-8.

XI. CONCLUSION

For the reasons set forth above, Petitioner respectfully submits that it has established a reasonable likelihood of success with respect to the challenged claim and requests that this petition be granted.

The Commissioner is hereby authorized to charge all fees due in connection with this matter to Attorney Deposit Account 50-3081.

Dated: December 15, 2014

Respectfully submitted,
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Attachment A: Certificate of Service

CERTIFICATE OF SERVICE

I hereby certify that on this 15th day of December, 2014, a copy of this PETITION FOR INTER PARTES REVIEW and copies of all supporting materials and exhibits have been served by Express Mail on the following addresses for patent owner(s):

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**Attachment B: List of Evidence
and Exhibits Relied Upon in The Petition**

Exhibit	Reference
1001	U.S. Patent No. 8,329,172
1002	Declaration of Michael L. Grossbard, M.D., in Support of the Petition for Inter Partes Review of U.S. Patent. No. 8,329,172, dated Dec. 5, 2014
1003	ECOG 1496
1004	ECOG 4494
1005	McNeil, <i>Non-Hodgkin's Lymphoma Trials In Elderly Look Beyond CHOP</i> , Journal of the National Cancer Institute 90(4):266-267 (February 18, 1998)
1006	Unterhalt <i>et al.</i> , <i>Significant Prolongation of Disease Free Survival in Advanced Low Grade Non Hodgkin's Lymphomas (nhl) by Interferon Alpha Maintenance</i> , International Conference on Malignant Lymphoma (1996)
1007	Public Hearing Transcript, Biological Response Modifiers Advisory Committee, Center for Biological Evaluation and Research, Food and Drug Administration, nineteenth meeting (July 25, 1997), available at http://www.fda.gov/ohrms/dockets/ac/97/transcpt/3311t2.pdf

Exhibit	Reference
1008	Rituxan® Product Label (1997)
1009	McLaughlin <i>et. al.</i> , <i>Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program</i> , <i>J. Clinical Oncology</i> 16:2825-2833 (August 7, 1998)
1010	Cheson <i>et al.</i> , <i>Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin’s Lymphomas</i> , <i>J. Clinical Oncology</i> 17:1244-1253 (1999).
1011	Hiddemann, <i>Non-Hodgkin’s Lymphomas—Current Status of Therapy and Future Perspectives</i> , <i>European Journal of Cancer</i> 31A:2141-2145 (1995)
1012	Portlock and Rosenberg, <i>Combination Chemotherapy with Cyclophosphamide, Vincristine, and Prednisone in Advanced Non-Hodgkin’s Lymphomas</i> , <i>Cancer</i> 37:1275-1282 (1976)
1013	Definition of <i>Biological Therapy</i> , NCI Dictionary of Cancer Terms – National Cancer Institute, http://www.cancer.gov/dictionary?CdrID=45617
1014	Definition of <i>Tumor Burden</i> , NCI Dictionary of Cancer Terms – National

Exhibit	Reference
	Cancer Institute, http://www.cancer.gov/dictionary?CdrID=44627
1015	Definition of <i>Residual Disease</i> , NCI Dictionary of Cancer Terms – National Cancer Institute, http://www.cancer.gov/dictionary?CdrID=45869
1016	Definition of <i>Time to Progression</i> , NCI Dictionary of Cancer Terms – National Cancer Institute, http://www.cancer.gov/dictionary?CdrID=44783
1017	Definition of <i>Disease-Free Survival</i> , NCI Dictionary of Cancer Terms – National Cancer Institute, http://www.cancer.gov/dictionary?CdrID=44023
1018	Definition of <i>Progression-Free Survival</i> , NCI Dictionary of Cancer Terms – National Cancer Institute, http://www.cancer.gov/dictionary?CdrID=44782
1019	Definition of <i>Non-Hodgkin Lymphoma</i> , Non-Hodgkin Lymphoma Home Page – National Cancer Institute, http://www.cancer.gov/cancertopics/types/non-hodgkin
1020	<i>Facts 2013</i> , Leukemia and Lymphoma Society (2013), available at http://www.lls.org/content/nationalcontent/resourcecenter/freeeducation

Exhibit	Reference
	materials/generalcancer/pdf/facts.pdf
1021	<i>SEER Stat Fact Sheets: Non-Hodgkin Lymphoma</i> , National Cancer Institute, http://seer.cancer.gov/statfacts/html/nhl.html
1022	Active ECOG Protocols, https://web.archive.org/web/19980519084342/http://ecog.dfci.harvard.edu/~ecogdba/active_reports/Lymphoma.html (archived May 19, 1998)
1023	Gupta and Lister, <i>Current Management of Follicular Lymphoma</i> , <i>Current Opinion in Oncology</i> 8:360-365 (1996)
1024	Al-Ismail, <i>Combination chemotherapy Including Epirubicin for the Management of Non-Hodgkin's Lymphoma</i> , <i>European J. Cancer and Clinical Oncology</i> 23:1379-1384 (1987)
1025	Steward, <i>et al.</i> , <i>Maintenance Chlorambucil After CVP in the Management of Advanced State, Low-Grade Histologic Type Non-Hodgkin's Lymphoma</i> , <i>Cancer</i> 61:441-447 (1988)
1026	<i>Biological Therapy for Cancer Treatment</i> , <i>Stanford Cancer Center</i> , https://web.archive.org/web/20131617382400/http://cancer.stanford.edu/information/cancerTreatment/methods/biological.html
1027	<i>Biological Therapies: Using the Immune System to Treat Cancer</i> ,

Exhibit	Reference
	National Cancer Institute, http://web.archive.org/web/19980216091909/http://cancernet.nci.nih.gov/clinpdq/therapy/Biological_Therapies:___Using_the_Immune_System_To_Treat_Cancer.html (archived Feb. 16, 1998)
1028	Hoerni <i>et al.</i> , <i>Successful Maintenance Immunotherapy by BCG of Non-Hodgkin's Malignant Lymphomas: Results of a Controlled Trial</i> , British J. Haematology 42:507-514 (1979)
1029	Hoerni <i>et al.</i> , <i>Maintenance Immunotherapy with BCG in Non-Hodgkin's Malignant Lymphomas: a Progress Report of a Randomized Trial</i> , Recent Results in Cancer Research 80:92-97 (1982)
1030	Ravaud <i>et al.</i> , <i>Adjuvant Bacillus Calmette-Guerin Therapy in Non-Hodgkin's Malignant Lymphomas: Long-Term Results of a Randomized Trial in a Single Institution</i> . J. Clinical Oncology 8:608-614 (1990)
1031	Jones <i>et al.</i> , <i>Improved Complete Remission Rates and Survival for Patients with Large Cell Lymphoma Treated with Chemoimmunotherapy</i> , Cancer 51: 1083-1090 (1983)
1032	McLaughlin <i>et al.</i> , <i>Management of Patients with Nodular Lymphoma</i> , UT M.D. Anderson Clinical Conference on Cancer, 27:301-312 (1984)

Exhibit	Reference
1033	Aviles, <i>The role of Interferon as Maintenance Therapy in Malignant Lymphoma</i> , Medical Oncology 14:153-157 (1997)
1034	Solal-Celigny <i>et al.</i> , <i>Doxorubicin-Containing Regimen With or without Interferon Alfa-2b for Advanced follicular Lymphomas</i> , J. Clinical Oncology 16:2332-2338 (July 1998)
1035	Definition of <i>Myelosuppression</i> , NCI Dictionary of Cancer Terms – National Cancer Institute, http://www.cancer.gov/dictionary?cdrID=%2044173
1036	Kohler and Milstein, <i>Derivation of Specific Antibody-Producing Tissue culture and Tumor Lines by Cell Fusion</i> , European J. Immunology 6:511-519 (1976)
1037	Grillo-López, <i>The First Antibody Therapy for Cancer: a Personal Experience</i> , Expert Review of Anticancer Therapy Retrospective 13(4):399-406 (2013)
1038	Maloney <i>et al.</i> , <i>IDEC-C2B8: Results of a Phase I Multiple-Dose Trial in Patients With Relapsed Non-Hodgkin's Lymphoma</i> , J. Clinical Oncology 15:3266-3274 (1997)
1039	Maloney <i>et al.</i> , <i>IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal</i>

Exhibit	Reference
	<i>Antibody Therapy in Patients With Relapsed Low-Grade Non-Hodgkin's Lymphoma</i> , Blood 90(6):2188-2195 (1997)
1040	Hochster <i>et al.</i> , <i>Maintenance Rituximab After Cyclophosphamide, Vincristine, and Prednisone Prolongs Progression-Free Survival in Advanced Indolent Lymphoma: Results of the Randomized Phase III ECOG 1496 Study</i> . J. Clinical Oncology 27(10):1607-1614 (2009)
1041	Habermann <i>et al.</i> , <i>Rituximab-CHOP Versus CHOP Alone or With Maintenance Rituximab in Older Patients With Diffuse Large B-Cell Lymphoma</i> , J Clinical Oncology 24:3121-3127(2006)
1042	Van Oers <i>et al.</i> , <i>Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial</i> , Blood 108:3295-3301 (2006)
1043	Hainsworth <i>et al.</i> <i>Rituximab as First-Line and Maintenance Therapy for Patients With Indolent Non-Hodgkin's Lymphoma</i> , J. Clinical Oncology 20(20):4261-4267 (2002)
1044	Ghielmini <i>et al.</i> , <i>Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly X4 schedule</i> ,

Exhibit	Reference
	Blood 103(12): 4416-4423 (2004)
1045	Davis <i>et al.</i> , <i>Retreatments with RITUXANTM (Rituximab, Idec-C2B8) Have Significant Efficacy, Do Not Cause HAMA, and are a Viable Minimally Toxic Alternative in Relapsed or Refractory Non-Hodgkin's Lymphoma (NHL)</i> . Blood 90(10)(Supp. 1):509A Abstract 2269 (1997)
1046	Maloney <i>et al.</i> , <i>Phase 1 Clinical Trial Using Escalating Single-Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients With Recurrent B-Cell Lymphoma</i> , Blood 84(8):2457-2466 col. 1 (1994)
1047	IDEC and Genentech joint press release (1996)
1048	<i>ECOG 1496 Trial for Low-grade or Follicular Non-Hodgkin's Lymphoma (NHL) - RITUXAN® (Rituximab)</i> , Genentech USA, Inc., and Biogen Idec Inc., http://www.rituxan.com/hem/hcp/non-hodgkin/post-induction/ecog
1049	ClinicalTrials.gov report on the NCT00003204 (ECOG 1496) Clinical Trial (1/27/2014) http://clinicaltrials.gov/show/NCT00003204
1050	FDA Clinical Review of Rituximab (2006)
1051	<i>ECOG Institutions by Name</i> , http://web.archive.org/web/

Exhibit	Reference
	19980519084032/http://ecog.dfci.harvard.edu/~ecogdba/general/insts_by_name.html (archived May 19, 1998)
1052	White, <i>Rituximab Immunotherapy for Non-Hodgkin's Lymphoma</i> , <i>Cancer Biotherapy & Radiopharmaceuticals</i> 14(4): 241 (August 1997)
1053	<i>PDQ -- NCI's Comprehensive Cancer Database</i> , http://web.archive.org/web/19980116194104/http://cancernet.nci.nih.gov/pdq.htm (archived Jan. 16, 1998)
1054	Czuczman <i>et al.</i> , <i>Chemoimmunotherapy of Low-Grade Lymphoma with the Anti-CD20 Antibody IDEC-C2B8 in Combination with CHOP Chemotherapy</i> , <i>Cancer Investigation</i> 14(S1): 59-61 (1996).
1055	Aviles <i>et al.</i> , <i>Maintenance therapy with interferon alfa 2b in patients with diffuse large cell lymphoma</i> , <i>Investigational New Drugs</i> 10:351-355 (1992)
1056	Aviles <i>et al.</i> , <i>Interferon Alpha 2b as Maintenance Therapy in Low Grade Malignant Lymphoma Improves Duration of Remission and Survival</i> , <i>Leukemia and Lymphoma</i> 20:495-499 (1996)
1057	Documents from European Oppositions pertaining to Application no. 08005921.5 (Patent no. EP 1 974 747 B1), available at

Exhibit	Reference
	register.epo.org/application?number=EP08005921&lng=en&tab=doclist
1058	Specification, August 18, 2007, US Patent application 11840956
1059	US Provisional Patent Application no. 60/096,180
1060	Preliminary Amendment filed Oct. 31, 2007 for US Patent application 11840956
1061	Amendment and Reply under 35 C.F.R. 1.111 filed Aug 25, 2010 for US Patent application 11840956
1062	Office Action, May 11, 2010, US Patent application 11840956
1063	Office Action, Feb 29, 2012, US Patent application 11840956
1064	Applicant's Remarks/Arguments, May 22, 2012, US Patent application 11840956
1065	Hickish <i>et al.</i> , <i>Molecular monitoring of low grade non-Hodgkin's lymphoma by gene amplification</i> , Br. J. Cancer 64:1161-1163 (1991)
1066	Amendment Responsive to Examiner's Request filed Oct 28, 2011, for US Patent application 11840956
1067	Arranz <i>et al.</i> , <i>Role of Interferon Alfa-2b in the Induction and Maintenance Treatment of Low-Grade Non-Hodgkin's Lymphoma: Results From a Prospective, Multicenter Trial With Double</i>

Exhibit	Reference
	<i>Randomization</i> , J. Clinical Oncology 16:1538-1546 (April, 1998)
1068	Hiddemann <i>et al.</i> , <i>New Aspects in the Treatment of Advanced Low-Grade Non-Hodgkin's Lymphomas: Prednimustine/Mitoxantrone Versus Cyclophosphamide/Vincristine/Prednisone Followed by Interferon Alfa Versus Observation Only—A Preliminary Update of the German Low-Grade Lymphoma Study Group</i> , Seminars in Hematology, Vol 31, No 2, Suppl 3:32-35 (1994)
1069	Notice of Allowability, June 26, 2012, US Patent application 11840956