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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

BIOGEN IDEC, INC., and GENENTECH, INC.,

Plaintiffs,

vs.

GLAXOSMITHKLINE LLC and GLAXO GROUP LIMITED,

Defendants.

CASE NO. 10-CV-00608 BEN (BGS)

CLAIM CONSTRUCTION ORDER

In this patent infringement action, the parties seek construction of three pairs of claim terms found in U.S. Patent No. 7,682,612. This matter was heard on June 9, 2011. Having considered the papers filed by the parties and oral argument on the motion, the Court construes the terms as follows.

BACKGROUND

Leukemia is a cancer of the white blood cell. In chronic lymphocytic leukemia ("CLL"), white blood cells known as B cells, or B lymphocytes, become cancerous. CLL patients have markedly increased numbers of B lymphocytes in the blood and bone marrow, and often in the lymph nodes and spleen. CLL is often diagnosed by measuring the number of B lymphocytes circulating in the blood. Symptoms of CLL include fatigue, fevers, bruising, bleeding, and infections. These symptoms are caused by the decrease in the number of red blood cells and platelets. In addition, the lymph nodes and spleen may enlarge due to the accumulation of cancerous B lymphocytes in these organs. The decision to treat a CLL patient is based upon the diagnosis of symptoms. The goals of treating CLL

are to (1) reduce the symptoms of the disease and (2) reduce the signs[1] of the disease. Treatment may also strive to increase the overall survival time of the patient as well as extend the amount of time the patient stays without signs or symptoms between treatments.

On November 9, 1999, Plaintiffs Biogen Idec, Inc. and Genentech, Inc. applied for U.S. Patent No. 7,682,612, which was approved on March 23, 2010. The '612 patent claims methods of treating CLL. The claimed invention consists of administering patients Rituxan, chimeric[2] anti-CD20 antibodies that recognize CD20 (a protein found on the outside surface of B lymphocytes) and destroy the cells that have CD20 on their surface. Rituxan is used in combination with conventional fludarabine and cyclophosphamide chemotherapy regimens.

On October 26, 2009, Defendants GlaxoSmithKline LLC and Glaxo Group Limited obtained FDA approval for Arzerra, its competing drug for treating CLL. Arzerra is a fully-human anti-CD20 antibody that binds with greater affinity[3] than Rituxan. In addition, Arzerra binds to a different epitope[4] than Rituxan—a portion of the CD20 antigen that was previously believed to be located beneath the cell surface. Arzerra is administered independently of other active anti-cancer agents.

Plaintiffs bring this action for infringement of the '612 patent. Specifically, Plaintiffs allege that the administration of Arzerra infringes claims 1–4, 6, 8–10, 14–17, 20–22, and 58–60 of the '612 patent. The parties have submitted competing constructions for three pairs of claim terms found in the '612 patent.

DISCUSSION

I. LEGAL STANDARD

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (internal quotation marks omitted). Courts determine the meaning of disputed claim terms from

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[1] "Symptoms" refers to what the patient experiences, while "signs" refers to the objective findings based on physical examinations or other tests performed on the CLL patient.

[2] A "chimeric antibody" is an antibody made from antibodies of more than one animal species.

[3] The "affinity" is how tightly an antibody attaches to a cell.

[4] An "epitope" is the location on the cell where an antibody attaches.

the perspective of a person of ordinary skill in the art at the time the patent is filed. *Chamberlain Group, Inc. v. Lear Corp.*, 516 F.3d 1331, 1335 (Fed. Cir. 2008). Claim terms "are generally given their ordinary and customary meaning." *Phillips*, 415 F.3d at 1312 (internal quotation marks omitted).

When construing claim terms, the court should first look to sources in the intrinsic record. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). First, "the claims themselves provide substantial guidance as to the meaning of particular claim terms." *Phillips*, 415 F.3d at 1314. Second, the claims "must be read in view of the specification, of which they are a part." *Id.* at 1315 (internal quotation marks omitted). The specification is usually "dispositive," as "it is the single best guide to the meaning of a disputed term." *Id.* (internal quotation marks omitted). Third, the court should consider the patent's prosecution history, which is the record of proceedings before the Patent and Trademark Office ("PTO") and includes the prior art cited during the patent examination. *Id.* at 1317. However, "because the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and thus is less useful for claim construction purposes." *Id.*

If the intrinsic evidence resolves the ambiguity in the disputed claim terms, then "it is improper to rely on extrinsic evidence." *Vitronics*, 90 F.3d at 1583. If ambiguities in the claim terms remain, however, courts may consider extrinsic evidence. *Id.* at 1584. Extrinsic evidence includes expert testimony, inventor testimony, dictionaries, and scientific treatises. *Phillips*, 415 F.3d at 1317.

II. THE '612 PATENT

The '612 patent, entitled "Treatment of Hematologic Malignancies Associated with Circulating Tumor Cells Using Chimeric Anti-CD20 Antibody," was issued on March 23, 2010. Biogen and Genentech are the assignees of the '612 patent.

The disputed claim terms are found in claim 1. Claim 1 covers: "A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an *anti-CD20 antibody* to the patient in an *amount effective to treat the chronic lymphocytic leukemia*, wherein the method *does not include treatment with a radiolabeled anti-CD20 antibody*." (Pascal Decl., Exh. 1 ['612 Patent], at 7:63–67 (emphasis added).) The parties dispute three pairs of claim terms: (1) "amount effective to treat" / "effective to treat the chronic lymphocytic leukemia," (2) "anti-CD20 antibody" / "CD20-

binding fragment," and (3) "does not include treatment with a radiolabeled anti-CD20 antibody" / "radiation is not used." Each pair of terms will be addressed in turn.

A. "Amount Effective to Treat" / "Effective to Treat the Chronic Lymphocytic Leukemia"

The parties dispute the terms "amount effective to treat" and "effective to treat the chronic lymphocytic leukemia." Plaintiffs propose that the term "effective to treat the chronic lymphocytic leukemia" be construed, while Defendants propose that the term "amount effective to treat" be construed. Plaintiffs propose that the term be construed as "providing a positive clinical benefit to the chronic lymphocytic leukemia patient," while defendants propose that it be construed as "includes amount of compound that achieves a reduction in circulating tumor cells."

As a preliminary matter, Plaintiffs contend that Defendants artificially limit the term to "amount effective to treat," which divorces the phrase from CLL, the target disease. The PTO and the inventors defined and discussed the entire term "effective to treat the chronic lymphocytic leukemia" during the prosecution history, and the entire phrase was added to the claims in an amendment, as explained in more detail below. (Pascal Decl., Exh. 5, at BID0004763.) In addition, the goal of the claimed method is to treat CLL specifically, as also explained below. Accordingly, the entire term "effective to treat the chronic lymphocytic leukemia" will be construed. *See Exxon Chem. Patents, Inc. v. Lubrizol Corp.*, 64 F.3d 1553, 1557 (Fed Cir. 1995) (claims must be construed in their entirety).

Before determining how the term "effective to treat the chronic lymphocytic leukemia" should be construed, it is also important to clarify the difference between the parties' proposed constructions. The parties agree that "effective to treat the chronic lymphocytic leukemia" includes the amount of antibody that achieves a reduction in circulating tumor cells; the issue is whether a patient *must also* reach a positive clinical benefit in order for the treatment to be effective. (*See* Pl. Op. Br. at 11 ("The claim-construction dispute addresses whether it is sufficient for the drugs at issue here *merely* to achieve a reduction in circulating tumor cells. Plaintiffs' construction . . . requires providing the patient with a positive clinical benefit that is directly related to the disease." (emphasis added)); Def. Op. Br. at 10 ("[Defendant]'s proposed construction does not foreclose the term 'amount effective to treat' from including treatment that results in partial or full remission of the disease, *i.e.*, positive

clinical benefit (according to plaintiffs). Rather, [Defendants] object[] to plaintiffs' limitation of the claim language to mean *only* treatment that results in a positive clinical benefit, (*i.e.*, partial or complete remission).").) At times, Defendants suggest that Plaintiffs' proposed construction excludes achieving a reduction in circulating tumor cells. (*See, e.g.*, Def. Op. Br. at 15 ("[P]laintiffs and their expert suggest that 'effective to treat' as used in the claims *does not include* a reduction in circulating tumor cells." (emphasis added)).) Plaintiffs' proposed construction, however, recognizes that the disputed term includes a reduction in tumor cells.

In addition, "positive clinical benefit" must be defined. The PTO considered the 1996 National Cancer Institute ("NCI") Guidelines during prosecution, which provides such a definition. (Pascal Decl., Exh. 1 ['612 Patent], at 8 (citing Bruce D. Cheson et al., *National Cancer Institute—Sponsored Working Group Guidelines for Chronic Lymphocytic Leukemia: Revised Guidelines for Diagnosis and Treatment*, 87 BLOOD 4990 (1996)).) The Guidelines explain that "[r]esponses that should be considered clinically beneficial include CR [complete remission], nPR [nodular partial remission] and PR [partial remission]; all others, e.g. stable disease, nonresponse, progressive disease, and death from any cause, should be rated as treatment failure." (Coutré Decl., Exh. C, at BID0001050, § 5.5.)

1. Specification

To construe "effective to treat the chronic lymphocytic leukemia," the Court will first look to the specification. The specification provides several examples which are "intended to provide clinical evidence in support of the efficacy of the invention." (Pascal Decl., Exh. 1 ['612 Patent], at 4:23–25.) In Example 1, four of the described patients experienced a reduction in circulating tumor cells. (*Id.* at 4:44–46.) The treatment of these four patients was ineffective, however, as they did not also experience a positive clinical benefit; they experienced severe toxic reactions to the anti-CD20 antibody, including fever, rigors, and bronchospasm with associated hypoxemia, and required hospitalization. (*Id.* at 4:40–55.) Although Defendants argue that the administration of anti-CD20 antibodies can cause infusion-related reactions in over 25% of cases in clinical trials, Example 1 describes the patients' reaction as a "unique syndrome of severe infusion-related reactions." (*Id.* at 4:41–42.) In addition, "[t]hrombocytopenia, a finding *not* commonly associated with RITUXAN® (rituximab) therapy, was noted in all four patients . . . , requiring transfusion in one case." (*Id.* at 4:48–53 (emphasis added).) These ineffective treatments are contrasted with "[t]wo subsequent

patients with CLL [who] have been treated with high blood tumor counts utilizing stepped-up dosing . . . with *demonstrated efficacy*, thrombocytopenia but minimal infusion-related toxicity." (*Id.* at 4:56–60 (emphasis added).)[5]

Example 3 provides an example of effective treatment of CLL. In this example, "[o]ne patient ha[d] progressive lymphocytosis on treatment and all other patients had reduction in peripheral blood lymphocytosis but less effect on lymph nodes." (*Id.* at 6:24–27.) Although "[t]wo patients developed severe hypertension with the first dose," "[t]oxicity at subsequent escalated dosages has been mild." (*Id.* at 6:18–20.) In addition, one patient achieved full remission, a positive clinical benefit. (*Id.* at 6:24.) In addition, Example 5 describes a clinical study for CLL patients combining administration of the anti-CD20 antibody with chemotherapy. (*Id.* at 7:5–55.) The goals of this study were "complete response (CR)," "partial response (PR)," and achieving progression-free survival and overall survival—all positive clinical benefits. (*Id.* at 7:41–55.)

Defendants point to U.S. Patent No. 5,736,137, which is incorporated by reference into the specification of the '612 patent. (*See id.* at 3:23–24.) The '137 patent describes the effective treatment of B-cell disorders with anti-CD20 antibodies as including the depletion of peripheral blood B-cells and the depletion of B-cells from lymph nodes and other tissue sources. (Def. Op. Br., Exh. N ['137 Patent], at 8:49–56 ("[A] series of events take place, each event being viewed by us as important to effective treatment of the disease. The first 'event' then, can be viewed as principally directed to substantially depleting the patient's peripheral blood B cells; the subsequent 'events' can be viewed as either principally directed to simultaneously or serially clearing remaining B cells from the system.").) Defendants argue that this demonstrates that depletion of B-cells is a key event to treating B-cell cancers, including CLL. Defendants are correct that depletion of tumor cells is a key event in treating CLL. This does not mean, however, that effective treatment of CLL does not also require a positive clinical benefit.

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[5] Defendants point to the Applicants' statement to the PTO that "the specification provides at least two examples with report data from *in vivo* trials to illustrate the efficacy of the antibody treatment for patients suffering from hematological malignancies," citing to Examples 1 and 3. (Def. Op. Br., Exh. A-13, at BID0005177–78.) This Amendment and Reply, however, is dated August 29, 2000. This was before the claims were amended in August 2006 by replacing "effective to achieve a reduction in circulating tumor cells" with "effective to treat the chronic lymphocytic leukemia." The Amendment and Reply is therefore not relevant to this analysis.

Defendants also point to various sections of the specification that describe the invention as treating malignancies associated with circulating blood tumor cells, through administration of a therapeutically effective amount of rituximab. (Pascal Decl., Exh. 1 ['612 Patent], at cover, 1:1–5, 15–20, 58–61; 2:16–20, 35–38; 3:48–54.) It is true that the '612 patent treats malignancies associated with circulating blood tumor cells, through administration of a therapeutically effective amount of rituximab. Specifying that the invention calls for the administration of a "therapeutically effective" amount of rituximab, however, does not imply that effective treatment of CLL includes *only* the reduction of circulating tumor cells, and not a positive clinical benefit. In addition, many of the portions of the specification to which Defendants cite refer to the originally filed, but later cancelled, claims. Statements in the specification relating to limitations in originally-filed claims are not relevant when the claims as issued recite no such limitation. *Spine Solutions, Inc. v. Medtronic Sofamor Danek USA, Inc.*, 620 F.3d 1305, 1315 (Fed. Cir. 2010).

2. Prosecution History

Second, the Court will look to the prosecution history. As originally filed in 1999, claim 1 read: "A method of treating a *hematologic malignancy* associated with high numbers of circulating tumor cells by administering a therapeutically effective amount of an anti-CD20 antibody or fragment thereof." (Pascal Decl., Exh. 5, at BID0004763.) On August 29, 2000, claim 1 was amended in response to a rejection. As amended, claim 1 read: "A method of treating *hematologic malignancy* associated with high numbers of circulating tumor cells by administering a therapeutically effective amount of an anti-CD20 antibody or antigen binding fragment thereof, said amount being *effective to achieve a reduction in circulating tumor cells*." (*Id.*, Exh. 13, at BID0005168 (emphasis added).) The goal of the claims early in the prosecution history, therefore, was to (1) treat a broad range of blood cancers, and (2) achieve a reduction in circulating tumor cells.

On August 7, 2006, in response to the Examiner's rejection of the claims as filed, the Applicants cancelled the claims for treating hematologic malignancies and replaced them with a new set of claims directed toward the treatment of CLL. The new claims required treatment to be "effective to treat the chronic lymphocytic leukemia," rather than "effective to achieve a reduction in circulating tumor cells." For instance, new application claim 29, which was issued as claim 1, read: "A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an unlabeled

anti-CD20 antibody to the patient in an amount *effective to treat the chronic lymphocytic leukemia.*" (*Id.*, Exh. 5, at BID0004751 (emphasis added).) In this response, the Applicants explained to the Examiner the difference between the original claims and amended claims: "The new claims also differ from the claims they replace in that the amount of anti-CD20 antibody administered to the patient is required to be 'effective to treat the chronic lymphocytic leukemia,' instead of 'effective to achieve a reduction in circulating tumor cells.'" (*Id.* at BID0004763.)[6]

In a May 29, 2009 Reply to the PTO, the Applicants further explained that "effective treatment of CLL must result in a *positive clinical benefit* to the CLL patient. . . . [T]he claims do require a specific, positive therapeutic outcome, and not simply induction of any type of response in the patient." (*Id.*, Exh. 3, at BID0000278 (emphasis added) (internal quotation marks omitted).) The Applicants went on to distinguish this limitation from an ineffective treatment described by Jensen in a 1998 scientific article[7] on treating CLL. (*Id.*) In *Jensen*, a CLL patient showed signs of progression of the disease, exhibited a severe adverse reaction, and had to be treated by a different therapy. (*Id.*, Exh. 6, at BID0000319–21.) The Applicants explained that "the requirements of the claims are not met by *Jensen*, as by no measure can an undesirable and life-threatening condition in the CLL patient, coupled with a continued progression of the CLL disease be considered an effective treatment of CLL." (*Id.*, Exh. 3, at BID0000278 (internal quotation marks omitted).)[8]

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[6] Defendants cite this August 2006 response as well, pointing out that the Applicants stated that their proposed claims are "directed specifically to the treatment of CLL" and that one skilled in the art "would understand that effective treatments of CLL include, but are *not necessarily limited to*, those assessed with respect to a reduction in circulating tumor cells." (Def. Op. Br., Exh. E, at BID0004763 (emphasis added).) This statement does not contradict Plaintiffs' construction; Plaintiffs do not argue that "effective to treat the chronic lymphocytic leukemia" does *not* include a reduction in tumor cells, but rather that it *also* includes a positive clinical benefit. In addition, as explained above, this same response makes clear that the new claims were directed to a new goal, different from "a reduction in circulating tumor cells." (*Id.*)

[7] M. Jensen et al., *Rapid Tumor Lysis in a Patient with B-Cell Chronic Lymphocytic Leukemia and Lymphocytosis Treated with an Anti-CD20 Monoclonal Antibody (IDEC-C2B8, Rituximab)*, 77 ANN HEMATOL 89 (1998).

[8] Defendants argue that each of the patients discussed in *Jensen* received rituximab in dosages claimed in the '612 patent. The patent, however, does not contemplate the same dosages being effective for every patient. The specification explains, "[e]ffective dosages will depend on the specific antibody, condition of the patient, age, weight, or any other treatments, among other factors. Typically effective dosages will range from about 0.001 to about 30 mg/kg body weight, more preferably from about 0.01 to 25 mg/kg body weight, and most preferably from about 0.1 to about 20 mg/kg body weight." (Pascal Decl., Exh. 1 ['612 Patent], at 3:48–54.)

Attached to this May 2009 Reply to the PTO, the Applicants included a declaration from Dr. David Schenkein, a practicing hematologist/oncologist at the time of the invention. Dr. Schenkein explained that "in an amount effective to treat the CLL" means that "the treatment must result in a positive clinical benefit to the CLL patient," and "refers to treatment methods that result in, for example, demonstrated efficacy with minimal infusion-related toxity . . . , overall response rate (ORR), complete responses (CR), partial responses (PR), improved median time to progression or improved duration of response . . . , or remission upon treatment." (*Id.*, Exh. 7, at BID0000293–94, ¶¶ 33–34.) Each of these examples cites to relevant descriptions in the specification. (*Id.*)

The PTO eventually issued the '612 patent, which contained claims directed toward methods of "administering an anti-CD20 antibody to the patient in an *amount effective to treat the chronic lymphocytic leukemia*." (*Id.*, Exh. 1 ['612 Patent], at 7:64–66 (emphasis added).) The prosecution history, therefore, supports construing the term "effective to treat the chronic lymphocytic leukemia" as "providing a positive clinical benefit to the chronic lymphocytic leukemia patient." *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 733–34 (2002) ("[C]laims are interpreted by reference to those that have been cancelled or rejected. . . . [B]y the amendment the patentee recognized and emphasized the difference between the two phrases, and the difference which the patentee thus disclaimed must be regarded as material." (internal quotation marks omitted)).

Defendants point to various sources that they argue support their proposed construction. Many of the sources Defendants cite, however, should not be considered by the Court. For instance, Defendants cite the August 2000 Amendment and Reply. This Amendment and Reply relate to the cancelled claims, which contain the "effective to achieve a reduction in circulating tumor cells" language. (*See* Def. Op. Br., Exh. A-13, at BID0005168.) In addition, Defendants cite an email written by Dr. John Byrd (who is not an inventor of the '612 patent), a scientific meeting abstract written by Byrd and inventor Christine White (among others), and a scientific article written by Byrd and White (among others). (*Id.*, Exhs. G, H, I.) These sources, however, are extrinsic evidence that should not be considered if the ambiguity in the claim terms is resolved by the intrinsic evidence. *See Vitronics*, 90 F.3d at 1583 (explaining that if the intrinsic evidence resolves the ambiguity in the disputed claim terms, then "it is improper to rely on extrinsic evidence"); *N. Am. Vaccine, Inc. v. Am. Cyanamid Co.*, 7 F.3d 1571, 1578 (Fed. Cir. 1993) ("A patent is to be interpreted by what it states

rather than by what the inventor wrote in a scientific publication."); *Saso Golf, Inc. v. Nike, Inc.*, No. 08 C 1110, 2010 WL 4481772, at *3 (N.D. Ill. Nov. 1, 2010) (disregarding statements by third parties in its claim construction analysis).

Finally, Defendants argue that Plaintiffs' proposed construction is untenable. Defendants argue that other courts have rejected claim constructions that require a clinical response in a patient. None of the cases Defendants cite support this proposition, however. The courts in two of the cases Defendants cite chose constructions that were specific to the statements made in the specification and prosecution history for the patents at issue there, and so are not applicable to the present case. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1300–03 (Fed. Cir. 2006); *Wyeth v. Abbott Labs.*, No. 08-230 (JAP), 08-1021 (JAP), 2010 WL 3001913, at *6–7 (D. N.J. July 28, 2010). In addition, *Seroctin Research & Technologies v. Unigen Pharmaceuticals* supports Plaintiffs' proposed construction, as the court construed the term "therapeutically effective amount" as "a quantity that produces a *positive result* in the treatment of depression/mood disorders." *Seroctin Research & Techs. v. Unigen Pharm.*, No. 2:07-cv-00582-TC, 2008 WL 4866008, at *3 (D. Utah Nov. 10, 2008) (emphasis added).

In light of both the specification and the prosecution history,[9] the term "effective to treat the chronic lymphocytic leukemia" shall be construed as "providing a positive clinical benefit to the chronic lymphocytic leukemia patient."

B. "Anti-CD20 Antibody" / "CD20-Binding Fragment"

The parties dispute the terms "anti-CD20 antibody" and "CD20-binding fragment." Plaintiffs propose that "anti-CD20 antibody" should be construed as "an antibody that binds to a cell surface CD20 antigen," and "CD20-binding fragment" should be construed as "a portion of an anti-CD20 antibody that binds to a cell surface CD20 antigen." Defendants propose that "anti-CD20 antibody" should be construed as "rituximab and antibodies that bind to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab," and "CD20-binding fragment" should be construed as "the portion of the anti-CD20 antibody that binds to the same epitope of the CD20 antigen with

[9] Both Plaintiffs and Defendants also point to extrinsic evidence in support of their proposed constructions. As the intrinsic evidence resolves the ambiguity in the claim terms, however, extrinsic evidence need not be considered.

similar affinity and specificity as rituximab."

The claims and the specification do not provide much guidance for whether the terms refer to an antibody or fragment thereof that binds to a particular epitope of the CD20 antigen with a particular affinity and specificity. The specification explains that the invention "provide[s] a novel treatment for . . . chronic lymphocytic leukemia (CLL) . . . comprising the administration of an anti-CD20 antibody." (Pascal Decl., Exh. 1 ['612 Patent], at 2:4–8.) The anti-CD20 antibody binds CD20, a protein found on the surface of the B lymphocytes. (*Id.* at 1:23–28.) The anti-CD20 antibody may be chimeric, primate, primatized, human, or humanized.[10] (*Id.* at 2:48–50.) "In the preferred embodiment, the anti-CD20 antibody will bind CD20 with high affinity, i.e., ranging from 10^{-5} to 10^{-9} M." (*Id.* at 2:45–47.) In addition, "a particularly preferred chimeric anti-CD20 antibody is RITUXAN® (rituximab)." (*Id.* at 3:18–19.) However, the Court may not "read[] limitations into a claim from the preferred embodiment described in the specification, even if it is the only embodiment described, absent clear disclaimer in the specification." *In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1369 (Fed. Cir. 2004).

The clearest evidence of the meaning of "anti-CD20 antibody" and "CD20-binding fragment" comes from the prosecution history. In a February 2000 Office Action, the PTO rejected claims 1 to 12 under 35 U.S.C. § 112 because "the specification, does not reasonably provide enablement commensurate with the scope of the claimed invention." (Pascal Decl., Exh. 12, at BID0005239.) Under Section 112,

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

35 U.S.C. § 112. In explanation, the Examiner pointed to the seemingly broad definition of "anti-CD20 antibody" and "CD20-binding fragment" in the specification. First, the Examiner explained that "Claims 1 and 12 are broadly drawn to '. . . an anti-CD20 antibody or fragment therefore'. This is broadly interpreted for examination purposes to be any and all anti-CD20 antibodies, no matter the

[10] A "humanized antibody" is a mostly human antibody with some non-human parts.

specificity or affinity for the specific epitope on the circulating tumor cells. While the specification is enabling for the application of RITUXAN®, RITUXIMAB® and 2B8-MX-DTPA in the treatment of hematologic malignancies, the specification is not enabling in the application of all other anti-CD20 antibodies, which may have different structural and functional properties." (Pascal Decl., Exh. 12, at BID0005239.) Second, the Examiner noted that "[t]he specification is silent concerning what sort of specificity and affinity would be necessary for the antibodies of the claimed passive immunotherapy so that one skilled in the art would not be able to practice the claimed invention without undue experimentation." (*Id.*)

In their August 29, 2000 Amendment and Reply, the Applicants traversed the rejection by arguing that they understood that the claim language did *not* encompass all anti-CD20 antibodies, but rather was limited to antibodies with a specificity and affinity similar to Rituxan. The Applicants argued that "even though antibodies directed to the same antigen might have different affinities and functional characteristics, one of skill in the art could readily identify an antibody that binds to CD20 with similar affinity and specificity as does RITUXAN® using techniques that are well known in the art." (*Id.*, Exh. 13, at BID0005174.) In addition, the Applicants pointed out that "the specification defines the preferred antibody . . . as one that binds CD20 with an affinity ranging from 10^{-5} to 10^{-9} M. Moreover, it is clear from the disclosure that the specificity must be such that antibody therapy results in a reduction of circulating tumor cells. Thus, the affinity and specificity of the antibodies to be used in the present invention are made clear in the disclosure." (*Id.* at BID0005175–76.)[11] The Examiner accepted these arguments, and in the next substantive Office Action withdrew the rejection. (*Id.*, Exh. 14, at BID0005125.) The prosecution history establishes that "anti-CD20 antibody" and "CD20-binding fragment" are defined as anti-CD20 antibodies or fragments thereof that bind to the CD20 antigen with similar affinity and specificity as rituximab. *See Teleflex, Inc. v. Ficosa N. Am. Corp.*,

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[11] Plaintiffs argue that in this same response, the Applicants explained that many types of anti-CD20 antibodies could be made for use with the invention, including chimeric, primate, primatized, humanized, and human antibodies. (Pascal Decl., Exh. 13, at BID0005176.) In addition, the Applicants stated that "the novelty of the presently claimed invention does not lie in a method of making therapeutic antibodies (although antibodies to be designed in the future for use in the claimed methods would certainly be encompassed)." (*Id.*) These statements, however, refer to the methods for producing chimeric, primate, primatized, humanized, and human antibodies. They do not establish that the claim language encompasses antibodies that bind with a different affinity and specificity than Rituximab, especially when considered in the context of the entire response.

299 F.3d 1313, 1326 (Fed. Cir. 2002) (holding that the prosecution history may "limit[] the interpretation of claims so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution in order to obtain claim allowance" (internal quotation marks omitted)).

First, Plaintiffs argue that because claims 11, 12, and 14 are limited to chimeric antibodies, rituximab, and human antibodies, respectively, the independent claims—such as claim 1—are necessarily broader and not limited to these types of antibodies. (*See* Pascal Decl., Exh. 1 ['612 Patent], at 8:31–32, 33–34, 37–38.) It is true that "dependent claims are presumed to be of narrower scope than the independent claims from which they depend under the doctrine of claim differentiation." *Regents of Univ. of Cal. v. Dakocytomation Cal., Inc.*, 517 F.3d 1364, 1375 (Fed. Cir. 2008) (internal quotation marks omitted). On the other hand, "the presumption created by the doctrine of claim differentiation is not a hard and fast rule and will be overcome by a contrary construction dictated by the written description or prosecution history." *Id.* (internal quotation marks omitted). In this case, any presumption created by the doctrine of claim differentiation is overcome by the construction dictated by the prosecution history discussed above.

Second, Plaintiffs point to prior art in support of their construction. For one, Plaintiffs point to U.S. Patent No. 5,736,137, incorporated by reference into the '612 patent at 3:23–24. (Pascal Decl., Exh. 15.) Plaintiffs argue that the '137 patent did not limit the definition of anti-CD20 antibody to Rituxan and other antibodies that bind a particular epitope of the CD20 protein. During prosecution, however, the Applicants argued that using the invention described in the '137 patent, "the skilled artisan could readily produce anti-CD20 antibodies using similar techniques, and screen such antibodies for those having an *affinity and functional activity similar to RITUXAN®*." (*Id.*, Exh. 13, at BID0005174–75 (emphasis added).) In addition, Plaintiffs point to U.S. Patent No. 5,776,456 (*id.*, Exh. 16, at 6:60–64), U.S. Patent No. 5,843,439 (*id.*, Exh. 17, at 6:1–5), U.S. Patent No. 6,682,734 (*id.*, Exh. 18, at 5:66–6:3), and the Einfeld reference (*id.*, Exh. 19, at 711)—all considered by the PTO during prosecution— arguing that they provide definitions of "anti-CD20 antibody" that do not refer to a particular specificity, affinity, or epitope. These sources, however, do not exclude a particular specificity, affinity, or epitope from the definition of "anti-CD20 antibody."

Third, Plaintiffs argue that because claims may capture after-arising technology, if drafted broadly enough, the construction of "anti-CD20 antibody" and "CD20-binding fragment" is not limited

to anti-CD20 antibodies or fragments thereof that bind to the same epitope of the CD20 antigen as rituximab. In 1998, at the time of the invention, it was believed that CD20 had only one extracellular region, or epitope, (i.e., the "large loop") to which CD20 antibodies could bind. Consequently, all antibodies that bound with a similar affinity and specificity as Rituxan at the time of the invention would have been understood to bind to this epitope. Not until 2006 was it discovered that Arzerra, a human antibody, could bind to a previously unknown epitope of the CD20 antigen, with a different affinity and specificity than rituximab.[12] Whether claim language may encompass after-arising technology, however, is irrelevant here. The prosecution history establishes that "anti-CD20 antibody" and "CD20-binding fragment" is defined as anti-CD20 antibodies or fragments thereof that bind to the CD20 antigen with similar affinity and specificity as rituximab. Antibodies that bind to the CD20 antigen with similar affinity and specificity as rituximab bind to the "large loop." Accordingly, the terms "anti-CD20 antibody" and "CD20-binding fragment" shall be construed as "rituximab and antibodies that bind to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab" and "the portion of the anti-CD20 antibody that binds to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab," respectively.

C. "Does Not Include Treatment with a Radiolabeled Anti-CD20 Antibody" / "Radiation Is Not Used"

The parties dispute whether the terms "does not include treatment with a radiolabeled[13] anti-CD20 antibody" and "radiation is not used" should be construed. Plaintiffs propose that no construction of these two terms is necessary, and their plain and ordinary meanings should be used. Defendants propose that "does not include treatment with a radiolabeled anti-CD20 antibody" should be construed as "excludes the use of a radiolabeled anti-CD20 antibody or the administration of a separate radiolabeled anti-CD20 antibody," and "radiation is not used" should be construed as "no form of radiation (including radiolabeled antibodies) is used."

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[12] In addition to binding the previously unknown epitope of the CD20 antigen, Arzerra also binds a portion of the "large loop" that Rituxan does not bind.

[13] A "radiolabeled antibody" is an antibody with a radioisotope attached to it. The radioisotope emits radiation.

Before amendment, pending claims 29 and 55 (issued claims 1 and 23) provided for the administration of an "unlabeled anti-CD20 antibody." (Def. Op. Br., Exh. B, at BID0001256, BID0001259.) The Examiner explained that pending claims 29 and 55, therefore, "could be interpreted to cover the administration of an unlabeled antibody followed by a radiolabeled antibody." (*Id.* at BID0001265.) The Applicants "discussed possible ways to amend the claims to exclude such a possibility." (*Id.*) "The examiner indicated amending the claims to exclude a step of administering a radiolabeled antibody would address the Office's concerns." (*Id.*)

Pending claims 29 and 55 were amended to read: "A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient . . . , *wherein the method does not include treatment with a radiolabeled antibody*." (*Id.* at BID0001256, BID0001259 (emphasis added).) The Applicants explained that "[pending] [c]laims 29 and 55 now require that the method does not include treatment with a radiolabeled antibody. This limitation expressly excludes the combination protocols described in the Kaminski patent, and it also precludes the use of a radiolabeled antibody as the anti-CD20 antibody of the recited administration step." (*Id.* at BID0001267.) The combination protocol described in the Kaminski patent includes the administration of an unlabeled antibody and the administration of a radiolabeled antibody. (*Id.* at BID0001269.) The claim language, therefore, excludes two separate treatments: (1) administration of an anti-CD20 antibody with a radiolabel attached to that antibody, and (2) administration of an anti-CD20 antibody that does not have a radiolabel along with the administration of a radiolabeled anti-CD20 antibody. Accordingly, the prosecution history supports Defendants' proposed constructions, "excludes the use of a radiolabeled anti-CD20 antibody or the administration of a separate radiolabeled anti-CD20 antibody" and "no form of radiation (including radiolabeled antibodies) is used." *See Edwards Lifescis. LLC v. Cook Inc.*, 582 F.3d 1322, 1329 (Fed. Cir. 2009) (applicants' arguments made to examiner regarding claim scope in light of prior art are controlling).

Plaintiffs argue that construction of these claim terms is inappropriate because the claim terms are straightforward, Defendants' proposed constructions complicate the terms and add redundancies, and Defendants' proposed constructions improperly seek an advisory opinion as to whether use of Arzerra with Bexxar or Zevalin would infringe the '612 patent. On the contrary, if the claims are not

construed, it would be unclear whether it would be within the scope of the claims to administer an unlabeled antibody followed by a radiolabeled antibody. A construction reflecting the understanding of the Applicants and the Examiner that the claims do not cover the administration of an unlabeled anti-CD20 antibody along with the administration of a radiolabeled anti-CD20 antibody, is neither unnecessary or improper.

In addition, Plaintiffs argue that Defendants' construction improperly seeks to exclude the use of a radiolabeled anti-CD20 antibody at any time in the patient's history or future care. Plaintiffs explain that "'[e]xcludes' implies that the claimed method would *actively* exclude treatment with a radiolabeled anti-CD20 antibody, *i.e.*, a method that specifically instructs a user not to use a radiolabeled anti-CD20 antibody." (Pl. Op. Br. at 24.) On the contrary, the Applicants used the term "excludes" when discussing the amendment of pending claims 29 and 55 with the PTO. (Def. Op. Br., Exh. B, at BID0001267 ("[Pending] [c]laims 29 and 55 now require that the method does not include treatment with a radiolabeled antibody. This limitation expressly *excludes* the combination protocols described in the Kaminski patent, and it also precludes the use of a radiolabeled antibody as the anti-CD20 antibody of the recited administration step." (emphasis added)).) In addition, this interpretation of Defendants' construction is divorced from the claim language. The claims are directed toward the treatment of a patient with an anti-CD20 antibody, not toward the treatments of the patient over his entire lifetime. (*See* Pascal Decl., Exh. 22, at BID0000164 ("[Pending] [c]laims 29 and 55 are amended to specify the *treatments* do not include the administration of a radiolabeled anti-CD20 antibody." (emphasis added)); *Id.*, Exh. 1 ['612 Patent], at 2:35–40.) Accordingly, the terms "does not include treatment with a radiolabeled anti-CD20 antibody" and "radiation is not used" shall be construed as "excludes the use of a radiolabeled anti-CD20 antibody or the administration of a separate radiolabeled anti-CD20 antibody," and "no form of radiation (including radiolabeled antibodies) is used," respectively.

CONCLUSION

For the reasons stated above, the term "effective to treat the chronic lymphocytic leukemia" shall be construed as "providing a positive clinical benefit to the chronic lymphocytic leukemia patient." The terms "anti-CD20 antibody" and "CD20-binding fragment" shall be construed as

"rituximab and antibodies that bind to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab" and "the portion of the anti-CD20 antibody that binds to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab," respectively. Lastly, the terms "does not include treatment with a radiolabeled anti-CD20 antibody" and "radiation is not used" shall be construed as "excludes the use of a radiolabeled anti-CD20 antibody or the administration of a separate radiolabeled anti-CD20 antibody," and "no form of radiation (including radiolabeled antibodies) is used," respectively.

IT IS SO ORDERED.

DATED: October 17, 2011

HON. ROGER T. BENITEZ
United States District Court Judge