



BlueCross BlueShield
of Alabama

Name of Policy:

Uses of Monoclonal Antibodies for the Treatment of Non-Hodgkin Lymphoma, including Chronic Lymphocytic Leukemia, and Acute Myeloid Leukemia in the Non-Hematopoietic Stem-Cell Transplant Setting

Policy #: 475

Category: Pharmacology

Latest Review Date: August 2014

Policy Grade: A

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

- 1. The technology must have final approval from the appropriate government regulatory bodies;*
- 2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
- 3. The technology must improve the net health outcome;*
- 4. The technology must be as beneficial as any established alternatives;*
- 5. The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

- 1. In accordance with generally accepted standards of medical practice; and*
- 2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
- 3. Not primarily for the convenience of the patient, physician or other health care provider; and*
- 4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Monoclonal antibodies targeted to cancer-associated antigens have been approved by the U.S. Food and Drug Administration (FDA) for various uses in oncology. In some cases, these agents are used in settings outside of the FDA-approved label, i.e., off-label use.

C20-Directed Cytolytic Antibodies

CD20 is a cell surface antigen expressed on pre B- and mature B-lymphocytes. More than 90% of malignant B-cells in non-Hodgkin lymphoma (NHL) express CD20. CD20-directed cytolytic antibodies mediate cell lysis by antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and induction of intracellular death signaling pathways (apoptosis). All three CD20-directed cytolytic antibodies carry black box warnings for hepatitis B virus reactivation and progressive multifocal leukoencephalopathy.

- Rituximab (Rituxan®) is a chimeric murine/human monoclonal antibody. In addition to inducing B-cell lysis, rituximab sensitizes B cells to the cytotoxic effects of chemotherapy. Rituximab also carries black box warnings for serious, potentially fatal, infusion reactions and severe mucocutaneous reactions.
- Ofatumumab (Arzerra®) is a fully human monoclonal antibody produced in a recombinant murine cell line. Ofatumumab targets an epitope that differs from the binding location of rituximab. In chronic lymphocytic leukemia (CLL), B cells underexpress CD20; unlike rituximab, which depends on CD20 expression for complement-dependent cytotoxicity, ofatumumab does not appear to depend on antigen intensity.
- Obinutuzumab (Gazyva™) is a humanized monoclonal antibody produced in Chinese hamster ovary cell culture. In addition to the cytolytic mechanisms described earlier, obinutuzumab induces antibody-dependent cellular phagocytosis.

Other Monoclonal Antibodies

Alemtuzumab (Campath®) is a recombinant, humanized, monoclonal antibody directed against the cell surface protein CD52, which is expressed on most normal and malignant B and T lymphocytes but not on hematopoietic stem cells. Therefore, alemtuzumab has the potential for broad application in treating B and T cell malignancies. Its mechanism of action appears to involve complement-mediated cell lysis, antibody-dependent cellular toxicity, and induction of apoptosis.

Gemtuzumab (Mylotarg®) is a recombinant, humanized monoclonal antibody directed against the CD33 antigen, which is expressed on the surface of leukemic blasts in more than 80% of patients with acute myeloid leukemia (AML) and by normal cells committed to the myeloid lineage. CD33 is not found on pluripotent hematopoietic stem cells. Leukemic blasts internalize CD33 antigen-antibody complexes, leading to DNA double-strand breaks and cell death.

This policy considers labeled and off-labeled indications for rituximab, ofatumumab, obinutuzumab, alemtuzumab, and gemtuzumab in NHL and AML in the non-hematopoietic stem-cell transplant setting.

For other covered indications of Rituximab, see Policy #044 Non-Oncologic Uses of Rituximab (Rituxan®).

Policy:

Effective for dates of service on or after April 17, 2014:

Rituximab

Rituximab (Rituxan®) meets Blue Cross and Blue Shield of Alabama's medical criteria when used to treat patients with the following diagnoses:

- B-cell non-Hodgkin lymphoma (NHL) in any of the following clinical situations:
 - For follicular lymphoma:
 - as first-line therapy (as combination therapy or as monotherapy)
 - as second or subsequent therapy (as combination therapy or as monotherapy)
 - as single-agent maintenance therapy (first- or second-line) in patients who achieve a complete or partial response to Rituxan in combination with chemotherapy
 - When used with CHOP or other anthracycline-based chemotherapy as first-line treatment for patients with diffuse large B-cell lymphoma (DLBCL)
 - For recurrent, aggressive CD20-positive NHL
 - For previously untreated or relapsed/refractory mantle cell lymphoma
 - As combination therapy in previously untreated and previously treated B-cell chronic lymphocytic leukemia (B-CLL)
 - For primary central nervous system lymphoma (PCNSL) that is not responsive to standard therapies
- Refractory or relapsed hairy cell leukemia (HCL)
- Marginal Zone Lymphoma
- T-cell chronic lymphocytic leukemia (T-CLL)
- Waldenström's macroglobulinemia (lymphoplasmacytic lymphoma)
- CD20-positive Hodgkin's disease (monotherapy)

Ofatumumab

Ofatumumab (Arzerra®) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of CLL that is refractory to fludarabine and alemtuzumab.*

Ofatumumab (Arzerra®) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate.*

Ofatumumab (Arzerra®) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** as maintenance therapy in patients with CLL.

Ofatumumab (Arzerra®) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for the treatment of malignancies other than B-cell CLL.

Obinutuzumab

Obinutuzumab (Gazyva™) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of previously untreated B-cell CLL when used in combination with chlorambucil.*

Obinutuzumab (Gazyva™) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational for relapsed or refractory NHL.**

Alemtuzumab

Alemtuzumab (Campath®) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage as a single agent for the treatment of B-cell chronic lymphocytic leukemia (B-CLL)* in patients with a chromosome deletion of 17p [del (17p)] or in patients not suitable for treatment with fludarabine.

Alemtuzumab (Campath®) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational for the treatment of malignancies other than B-cell CLL.**

Gemtuzumab

Gemtuzumab ozogamicin (Mylotarg®) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of patients with CD33-positive acute myeloid leukemia (AML) in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy.

Note that in June 2010, Pfizer, Inc. announced the voluntary withdrawal of Mylotarg® (gemtuzumab ozogamicin) from the U.S. market. Patients who are currently receiving the drug may continue their planned course of therapy; however, Mylotarg® will not be commercially available to new patients.

Gemtuzumab ozogamicin (Mylotarg®) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational for:**

- Treatment of patients with AML and who are younger than 60 years of age;
- Treatment of newly diagnosed AML;
- Treatment of second or subsequent relapse of AML;
- Use in combination with cytotoxic chemotherapy.

*Indicates an indication approved by the U.S. Food and Drug Administration

Effective for dates of service November 3, 2013 through April 16, 2014:

Rituximab

Rituximab (Rituxan®) meets Blue Cross and Blue Shield of Alabama's medical criteria when used to treat patients with the following diagnoses:

- B-cell non-Hodgkin lymphoma (NHL) in any of the following clinical situations:
 - For follicular lymphoma:
 - as first-line therapy (as combination therapy or as monotherapy)

- as second or subsequent therapy (as combination therapy or as monotherapy)
- as single-agent maintenance therapy (first- or second-line) in patients who achieve a complete or partial response to Rituxan in combination with chemotherapy
- When used with CHOP or other anthracycline-based chemotherapy as first-line treatment for patients with diffuse large B-cell lymphoma (DLBCL)
- For recurrent, aggressive CD20-positive NHL
- For previously untreated or relapsed/refractory mantle cell lymphoma
- As combination therapy in previously untreated and previously treated B-cell chronic lymphocytic leukemia (B-CLL)
- For primary central nervous system lymphoma (PCNSL) that is not responsive to standard therapies
- Refractory or relapsed hairy cell leukemia (HCL)
- Marginal Zone Lymphoma
- T-cell chronic lymphocytic leukemia (T-CLL)
- Waldenström’s macroglobulinemia (lymphoplasmacytic lymphoma)
- CD20-positive Hodgkin’s disease (monotherapy)

Ofatumumab

Ofatumumab (Arzerra®) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the treatment of CLL that is refractory to fludarabine and alemtuzumab.*

Ofatumumab (Arzerra®) does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational** in previously untreated CLL or as maintenance therapy in patients with CLL.

Ofatumumab (Arzerra®) does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational** for the treatment of malignancies other than B-cell CLL.

Obinutuzumab

Obinutuzumab (Gazyva™) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the treatment of previously untreated B-cell CLL when used in combination with chlorambucil.*

Obinutuzumab (Gazyva™) does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational** for relapsed or refractory NHL.

Alemtuzumab

Alemtuzumab (Campath®) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage as a single agent for the treatment of B-cell chronic lymphocytic leukemia (B-CLL)* in patients with a chromosome deletion of 17p [del (17p)] or in patients not suitable for treatment with fludarabine.

Alemtuzumab (Campath®) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for the treatment of malignancies other than B-cell CLL.

Gemtuzumab

Gemtuzumab ozogamicin (Mylotarg®) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of patients with CD33-positive acute myeloid leukemia (AML) in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy.

Note that in June 2010, Pfizer, Inc. announced the voluntary withdrawal of Mylotarg® (gemtuzumab ozogamicin) from the U.S. market. Patients who are currently receiving the drug may continue their planned course of therapy; however, Mylotarg® will not be commercially available to new patients.

Gemtuzumab ozogamicin (Mylotarg®) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for:

- Treatment of patients with AML and who are younger than 60 years of age;
- Treatment of newly diagnosed AML;
- Treatment of second or subsequent relapse of AML;
- Use in combination with cytotoxic chemotherapy.

*Indicates an indication approved by the U.S. Food and Drug Administration

Effective for dates of service prior to November 3, 2013:

Rituximab

Rituximab (Rituxan®) meets Blue Cross and Blue Shield of Alabama's medical criteria when used to treat patients with the following diagnoses:

- B-cell non-Hodgkin lymphoma (NHL) in any of the following clinical situations:
 - For follicular lymphoma:
 - as first-line therapy (as combination therapy or as monotherapy)
 - as second or subsequent therapy (as combination therapy or as monotherapy)
 - as single-agent maintenance therapy (first- or second-line) in patients who achieve a complete or partial response to Rituxan in combination with chemotherapy
 - When used with CHOP or other anthracycline-based chemotherapy as first-line treatment for patients with diffuse large B-cell lymphoma (DLBCL)
 - For recurrent, aggressive CD20-positive NHL
 - For previously untreated or relapsed/refractory mantle cell lymphoma
 - As combination therapy in previously untreated and previously treated B-cell chronic lymphocytic leukemia (B-CLL)
 - For primary central nervous system lymphoma (PCNSL) that is not responsive to standard therapies
- Refractory or relapsed hairy cell leukemia (HCL)

- Marginal Zone Lymphoma
- T-cell chronic lymphocytic leukemia (T-CLL)
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Ofatumumab

Ofatumumab (Arzerra®) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of CLL that is refractory to fludarabine and alemtuzumab.*

Ofatumumab (Arzerra®) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** in previously untreated CLL or as maintenance therapy in patients with CLL.

Obinutuzumab

Obinutuzumab (Gazyva™) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of previously untreated B-cell CLL when used in combination with chlorambucil.*

Obinutuzumab (Gazyva™) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for relapsed or refractory NHL.

Alemtuzumab

Alemtuzumab (Campath®) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage as a single agent for the treatment of B-cell chronic lymphocytic leukemia (B-CLL)* in patients with a chromosome deletion of 17p [del (17p)] or in patients not suitable for treatment with fludarabine.

Alemtuzumab (Campath®) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for the treatment of malignancies other than B-cell CLL.

Gemtuzumab

Gemtuzumab ozogamicin (Mylotarg®) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of patients with CD33-positive acute myeloid leukemia (AML) in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy.

Note that in June 2010, Pfizer, Inc. announced the voluntary withdrawal of Mylotarg® (gemtuzumab ozogamicin) from the U.S. market. Patients who are currently receiving the drug may continue their planned course of therapy; however, Mylotarg® will not be commercially available to new patients.

Gemtuzumab ozogamicin (Mylotarg®) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for:

- Treatment of patients with AML and who are younger than 60 years of age;
- Treatment of newly diagnosed AML;

- Treatment of second or subsequent relapse of AML;
- Use in combination with cytotoxic chemotherapy.

*Indicates an indication approved by the U.S. Food and Drug Administration

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The 2001 TEC Assessment addressed off-label uses of the monoclonal antibodies listed in this policy. The 2002 TEC Assessment specifically addressed the use of rituximab for treatment of intermediate and aggressive B-cell non-Hodgkin lymphoma (NHL; primarily diffuse large B-cell lymphoma [DLBCL]). It was based on one randomized, controlled trial (RCT) and three uncontrolled studies that supported the policy statement for this use. The policy has been updated periodically with literature searches of the MEDLINE (PubMed®) database. The most recent literature review is below.

Rituximab (Rituxan®)

First-line Treatment of Follicular Lymphoma (FL)

Several Phase III trials have evaluated the efficacy of rituximab in combination with various chemotherapy regimens as first-line therapy for indolent NHL/follicular lymphoma (FL). With the exception of one trial, the addition of rituximab in combination with several different chemotherapy regimens, including CHOP (cyclophosphamide, doxorubicin [Adriamycin], vincristine, prednisone), CVP (cyclophosphamide, vincristine, prednisone), and others, resulted in significantly greater complete remission (CR) (41–79% vs. 10–63%, respectively; $p < 0.005$), and greater overall response rates (81–96% vs. 57–90%, respectively; $p < 0.05$). The addition of rituximab to first- or second-line therapy with different chemotherapy regimens has shown variable results in improvement of overall survival (OS) rates in Phase III trials. However, a meta-analysis of OS data from four trials with a total of 1,015 patients with FL, showed significantly improved OS when rituximab was added to chemotherapy compared to chemotherapy alone (hazard ratio [HR] favoring treatment with the addition of rituximab (HR 0.57; 95% confidence interval [CI]: 0.43–0.77).

Hiddemann et al reported the results of front-line therapy in advanced-stage FL in 428 patients randomized to CHOP alone or rituximab plus CHOP (R-CHOP). In the patients who received R-CHOP, there was a significantly prolonged time to treatment failure ($p < 0.001$), a higher overall response rate (96% vs. 90%, respectively; $p = 0.011$), and a prolonged duration of remission ($p = 0.001$). Additional follow-up on a subset of the original study group (patients aged 60 years and older) showed a four-year progression-free survival (PFS) advantage of R-CHOP over

CHOP (62.2% vs. 27.9%, respectively; $p < 0.0001$,) and four-year OS (90% vs. 81%, respectively; $p = 0.039$).

Marcus et al randomly assigned previously untreated patients with advanced-stage FL to CVP ($n = 159$) or rituximab plus CVP (R-CVP; $n = 162$). Overall response and CR rates were 81% and 41%, respectively in the R-CVP arm versus 57% and 10%, respectively in the CVP arm, ($p < 0.0001$). After a median follow-up of 30 months, the patients who received R-CVP had a median time to progression of 32 months versus 15 for CVP only ($p < 0.0001$). The median time to treatment failure was 27 months for R-CVP versus seven months for CVP ($p < 0.0001$). An update of the study with a median follow-up of 53 months showed an improvement in OS in the R-CVP arm, with an estimated four-year OS of 83% versus 77% in the CVP arm ($p = 0.029$).

Although trials have shown improved outcomes combining rituximab with chemotherapy, the issue of which chemotherapy regimen to use as initial therapy for FL (e.g., CHOP versus CVP) is still being debated.

Relapsed/Refractory FL

The efficacy of rituximab as monotherapy in patients with relapsed or refractory low-grade FL has been examined in non-comparative multicenter trials, as summarized in a review article. Most trials included patients with low-grade or FL, and the majority of patients had Stage 3 or 4 disease. Where specified, the median duration of follow-up ranged from 173 days to 1.5 years. Across studies, baseline characteristics were median patient age 50-58 years, 34-63% of patients were male, and patients had received a median of two prior treatments (two studies), three prior treatments (three studies) or four prior treatments (one study). Number of patients ranged from 30 to 166 across studies. Overall response rates were 38-48% after four weeks of rituximab therapy and 57% after eight weeks of therapy. Complete remission rates ranged from 3% to 17%. The median duration of response ranged from 5.9-17.8 months, and the median time to progression was 8.1-16.3 months, after four weeks' therapy. Median duration of response and median time to progression had not yet been reached after a median 13.4 and 19.4 months' follow-up in patients who received eight weeks of rituximab therapy.

Maintenance Therapy in Previously Untreated FL

Salles et al report the results of a Phase 3 RCT (the PRIMA study) which was undertaken in 223 centers in 25 countries. The study assessed the potential benefit of two years of rituximab maintenance therapy after first-line treatment in patients with FL needing systemic therapy. A total of 1,217 patients received one of three non-randomized induction regimens consisting of rituximab and chemotherapy; 1,019 patients had a PR or CR and were then randomly assigned to receive either two years of rituximab maintenance therapy ($n = 505$) or observation ($n = 513$). The primary endpoint was PFS. After a median follow-up of 36 months, PFS was 74.9% (95% CI 70.9-78.9) in the rituximab maintenance group and 57.6% (53.2-62.0) in the observation group (HR 0.55, 95% CI 0.44-0.68; $p < 0.0001$). Two years after randomization, 71.5% of patients in the rituximab maintenance group were in CR versus 52.2% in the observation group ($p = 0.0001$). More patients who were in PR at the time of randomization converted to a CR after two years in the rituximab maintenance group (52%) than those in the observation group (30%); estimated difference 22.2%, 95% CI 11.2-33.3; $p = 0.0001$. There was a significant reduction in the risk of starting a new antilymphoma treatment or death or starting a new chemotherapy or death in the

maintenance group. Grade 3 and 4 adverse events were recorded in 24% of patients in the rituximab maintenance group and 17% in the observation group, with infections being the most common adverse event. OS did not differ significantly between groups; however, the authors state that since longer follow-up will be needed to show any possible effect of rituximab maintenance on OS, they would continue to follow these patients. The authors conclude that two years of rituximab maintenance therapy significantly prolongs PFS, delays the time to the next antilymphoma treatment and next chemotherapy, and improves the quality of the response in patients with previously untreated follicular lymphoma that is responsive to first-line rituximab plus chemotherapy.

Maintenance Therapy in Relapsed FL

In 2006, van Oers et al evaluated the role of rituximab in both induction and maintenance of relapsed/refractory FL. They randomized 465 patients to induction with six cycles of CHOP versus R-CHOP, with a second randomization of patients in CR or PR to rituximab maintenance or observation. Induction therapy that included rituximab yielded statistically significant improvement in overall response (85.1% vs. 72.3%; $p < 0.001$) and complete remission rates (29.5% vs. 15.6%; $p < 0.001$), and median PFS from first randomization (33.1 months vs. 20.2 – all respectively; $p < 0.001$). Rituximab maintenance resulted in a median PFS from second randomization of 51.5 months versus 14.9 months, respectively, with observation (HR: 0.40; $p < 0.001$). Rituximab maintenance also improved OS from the second randomization with OS rates of 85% in the rituximab arm versus 77% with observation alone at three years ($p = 0.011$). In 2010, van Oers et al reported on the long-term outcomes of maintenance in this same patient population, with a median follow-up of six years. Maintenance therapy with rituximab improved PFS compared with observation (median, 3.7 years versus 1.3 years, respectively; $p < 0.001$; HR, 0.55), both after CHOP induction ($p < 0.001$; HR, 0.37) and R-CHOP ($p = 0.003$; HR, 0.69). The five-year OS was 74% in the rituximab maintenance arm and 64% in the observation arm ($p = 0.07$). Rituximab maintenance was associated with a significant increase in Grade 3 and 4 infections (9.7% versus 2.4% respectively; $p = 0.01$). The authors concluded that the use of rituximab maintenance therapy in relapsed/resistant FL led to superior PFS and that although the improvement in OS did not reach statistical significance, this may have been due to an unbalanced use of rituximab in post-protocol salvage treatment (after disease progression, rituximab-containing salvage therapy was given to 59% of patients treated with CHOP followed by observation, compared with 26% after R-CHOP followed by rituximab maintenance).

Studies on Maintenance Therapy that Included Previously Untreated and Relapsed FL

In 2010, Martinelli et al reported the long-term follow-up of a randomized clinical trial comparing induction therapy with single-agent rituximab alone with or without prolonged maintenance therapy with rituximab in patients with FL. Patient population consisted of those who had received prior chemotherapy ($n = 138$) and those who were chemotherapy naïve ($n = 64$). All patients received single-agent rituximab and, if they did not progress, they were randomly assigned to no further treatment (observation arm) or four additional doses of rituximab given at two month intervals. Median follow-up was 9.5 years, with all living patients having been observed for at least five years. The median event-free survival (EFS) for the observation versus the maintenance group was 13 months versus 24 months, respectively ($p < 0.001$). Of the previously untreated patients, at eight years' follow-up, 45% of those who had received rituximab maintenance treatment after responding to rituximab induction ($n = 38$) were still

without event, compared to 22% in the observation group. The authors concluded that single agent rituximab and prolonged maintenance therapy with rituximab could result in long-term remission, particularly in patients who had received no prior treatment and responded to rituximab induction.

In 2009, Vidal et al performed a systematic review and meta-analysis of RCTs to evaluate the effect of maintenance rituximab on the OS of patients with FL. (The report did not include the above 2010 Martinelli et al study). The largest study included in the systematic review is outlined in further detail under maintenance therapy in relapsed FL. Five studies were included (total of 1,143 patients) that compared rituximab maintenance therapy with observation or treatment at relapse (no maintenance). One study included only patients with previously untreated FL, three included patients with relapsed FL, and one study included both previously untreated and relapsed FL. In three trials, patients were randomly assigned to a type of induction therapy and subsequently underwent a second randomization to maintenance therapy or observation. The other two trials consisted of patients treated with the same induction therapy who were then subsequently randomly assigned to maintenance therapy or observation. Data for 985 patients were available for the meta-analysis of OS. Patients with refractory or relapsed FL had a clear survival benefit with maintenance rituximab therapy compared to patients in the observation group (HR of death: 0.58; 95% CI 0.42-0.79; 4 trials). Among patients who were previously untreated, the survival benefit was not statistically significant (HR of death: 0.68; 95% CI 0.37-1.25; two trials). Grade 3 or 4 adverse effects were reported in three trials and were higher in the rituximab maintenance arm (risk ratio [RR]:1.52, 95% CI 1.00-2.30).

DLBCL and Other Aggressive NHL

Previously Untreated

The use of rituximab with a CHOP or CHOP-like regimen has been found to be more effective than chemotherapy alone as first-line treatment in patients with advanced-stage DLBCL and mantle-cell lymphoma (MCL) in several Phase III trials.

In 2010, Coiffier et al reported the long-term outcomes of a randomized study (LNH-98.5) involving 399 elderly patients (defined as aged 60–80 years) with previously untreated, diffuse, large B-cell lymphoma that were randomized to eight cycles of classical CHOP or R-CHOP. Median follow-up was ten years. Ten-year PFS was 36.5% (95% CI: 29.7–43.3%) with R-CHOP compared with 20% (95% CI: 14.6–26.2%) with CHOP only. Median OS was 8.4 years (95% CI 5.4-not reached) in the R-CHOP arm and 3.5 years (95% CI 2.2-5.5) in the CHOP arm (p<0.0001).

In 2008, Pfreundschuh et al reported the results of an RCT of 1,222 elderly (aged 61–80 years) patients with aggressive CD20+ NHL to six or eight cycles of CHOP (at two-week intervals, also known as CHOP-14), with or without rituximab, and showed a significant improvement in EFS, PFS, and OS in patients receiving R-CHOP versus CHOP. Three-year OS was 67.7% (62.0–73.5) for six cycles of CHOP-14, 66.0% (60.1–71.9) for eight cycles of CHOP-14, 78.1% (73.2–83.0) for six cycles of R-CHOP-14, and 72.5% (67.1–77.9) for eight cycles of R-CHOP-14. OS improved only after six cycles of R-CHOP-14 (RR 0.63 [0.46–0.85]; p=0.0031). The authors concluded that of the four regimens studied, six cycles of R-CHOP was the preferred treatment for elderly patients.

In 2006, Habermann et al reported a two-stage, randomized trial of 632 patients 60 years or older with untreated DLBCL. Patients were randomized to CHOP or R-CHOP, and 415 responders underwent a second random assignment to maintenance with rituximab or observation. Three-year failure-free survival (FFS) was 53% for R-CHOP and 46% for CHOP induction (HR: 0.78; 95% CI: 0.61 to 0.99; p=0.04). Two-year FFS rate after the second randomization for maintenance was 76% versus 61% for rituximab maintenance versus observation (p=0.009). A significant difference in the effect of the maintenance therapy with rituximab was seen according to the type of induction received, with maintenance rituximab significantly prolonging FFS after CHOP (HR: 0.45; 95% CI: 0.29–0.71; p=0.0004) but not after R-CHOP (HR: 0.93; 95% CI: 0.53–1.66; p=0.81). A secondary analysis was performed to evaluate the effect of induction therapy without maintenance rituximab. R-CHOP alone showed a significant decrease in the risk of treatment failure compared with CHOP (HR: 0.64; 95% CI: 0.47–0.85; p=0.003), with an estimated three-year FFS rate of 52% for R-CHOP and 39% for CHOP. Survival was also longer after R-CHOP induction alone, with an estimated three-year OS rate of 67% for R-CHOP versus 58% for CHOP (HR: 0.72; 95% CI: 0.52–1.00; p=0.05).

Recent use of molecular profiling has shown greater survival advantages with rituximab in certain histologically indistinguishable but distinctly different molecular subtypes of DLBCL. Future clinical trials may include molecular profiling to identify the most beneficial treatment combinations incorporating newer therapeutic agents such as rituximab.

Relapsed or Refractory

Several single-arm studies have examined chemoimmunotherapy regimens with rituximab for relapsed or refractory DLBCL. These are summarized in Table 1. Overall response rates were 33% to 62%. In two studies, patients who responded were eligible for stem-cell transplant.

Table 1: Studies of Rituximab Chemoimmunotherapy for Relapsed or Refractory DLBCL

Study	N	Patients	Treatment	Result
Omachi 2013	63	Transplant ineligible (86%) or relapse after transplant (14%)	Up to 6 (median, 4) 21-d cycles of rituximab 375 mg/m ² on day 1 plus bendamustine 120 mg/m ² IV on days 2 and 3	CR: 37% PR: 25% PFS ^a : 6.7 m
Gyan 2013	50	1st relapse	Three 28-d cycles of rituximab 375 mg/m ² on day 1 plus ifosfamide, vinorelbine, mitoxantrone, prednisone	CR: 30% PR: 11%
Wang 2013	45	DLBCL (71%), transformed LCL (20%), grade 3 FL (9%)	28-day cycles of rituximab 375 mg/m ² IV weekly for 4 wk during cycle 1 only plus lenalidomide 20 mg orally daily on days 1-21 (mean no. of cycles, 4)	CR: 22% PR: 11%

CR: complete response; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; IV: intravenous; LCL: large-cell lymphoma; PFS: progression-free survival; PR: partial response.

^a Median.

Mantle Cell Lymphoma (MCL)

In 2005, Romaguera et al published a prospective Phase 2 study of 97 patients who had newly diagnosed MCL and received rituximab plus hyper-cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD) alternating with high-dose methotrexate-cytarabine. Among 97 assessable patients, the response rate was 97% with a complete or unconfirmed CR rate of 87%.

At a median follow-up time of 40 months, three-year FFS was 64% and OS was 82%. Patients 65 years of age or younger had three-year FFS of 73%. Toxicity was significant and FFS shorter in patients older than 65 years of age. An update of this patient population with median follow-up of 4.8 years reported five-year FFS and OS of 48% and 65%, respectively.

In 2005, Lenz et al published the results of a prospective, randomized trial of 122 patients with previously untreated advanced stage MCL comparing CHOP chemotherapy alone versus R-CHOP. R-CHOP was superior in terms of overall response rate (94% vs. 75%, respectively; $p=0.0054$), CR rate (34% vs. 7%, respectively; $p=0.00024$), and time to treatment failure (median 21 vs. 14 months, respectively; $p=0.0131$). However, no differences were observed in PFS or OS between the two groups.

In 2004, Forstpointner et al published the results of a prospective, randomized, open-label multicenter Phase III trial comparing the use of fludarabine, cyclophosphamide, and mitoxantrone (FCM), with and without the addition of rituximab, in patients with relapsed and refractory follicular and MCL. The number of patients with MCL was 52, and the group that received FCM plus rituximab (R-FCM) showed a superior overall response rate of 58% versus 46%, respectively ($p=0.282$). A significantly longer OS was observed in the R-FCM group, with the median OS not reached at two years, versus an estimated median OS for the FCM group of 11 months ($p=0.0042$). At two years, the estimated OS in the R-FCM arm was 65%, compared with 35% in the FCM arm.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is a disease of the older population and tends to have a prolonged course. It is generally treated in a conservative fashion, and often treatment is initiated only when a patient becomes symptomatic as the disease progresses. Treatment of an individual patient may be variable and depend on age and other risk factors, including certain molecular abnormalities. As CLL is generally considered incurable, the aim of treatment often is to induce CR, including eliminating minimal residual disease in the bone marrow. Minimal residual disease is usually evaluated by sensitive testing methods, which include flow cytometry or polymerase chain reaction (PCR), with patients free of minimal residual disease following treatment having longer remission duration and survival.

Current chemotherapy options for CLL include alkylating agents such as chlorambucil or cyclophosphamide (which when used as single agents have shown CR rates of less than 10%) and purine analogs such as fludarabine (with single-agent CR rates of 20%). The combination of an alkylating agent and fludarabine improves the CR to 40%.

A 2012 Cochrane review compared the clinical benefits and harms of monoclonal anti-CD20 antibodies compared to no further treatment or to other anti-leukemic therapies in patients with CLL, irrespective of disease status. Both pre-treated and chemotherapy naïve patients with included, and all of the trials included in the review were randomized and open-label. Three RCTs ($n=1,421$) assessed the efficacy of rituximab plus chemotherapy compared to chemotherapy alone, and a meta-analysis found a statistically significant OS and PFS advantage for the patients who received rituximab. Although there were more Grade 3 and 4 adverse events in the rituximab arm, it did not lead to a statistically significant difference regarding treatment-

related mortality. Two RCTs (n=177) evaluated rituximab versus alemtuzumab; neither study reported PFS or OS. There was no statistically significant difference between arms regarding complete response rate or treatment-related mortality. However, more serious adverse events occurred in the alemtuzumab arm.

Previously Untreated CLL

In 2010, Halleck et al reported the results of a randomized, open-label, multicenter Phase 3 trial (CLL8 trial). Treatment-naïve patients with CLL were randomized to receive fludarabine and cyclophosphamide with (n=408) versus without (n=409) rituximab in 190 centers in 11 countries. At three years after randomization, 65% of patients in the chemoimmunotherapy group were free of progression versus 45% in the chemotherapy only group (HR 0.56 95% CI 0.46-0.69; p<0.0001), and 87% were alive versus 83%, respectively (HR 0.67 0.48-0.92; p=0.01). Chemoimmunotherapy was more frequently associated with Grade 3 and 4 neutropenia (34% versus 21%; p<0.0001) and leukopenia (24% versus 12%; p<0.0001); however, other side effects, including severe infections, were not increased. Treated-related deaths occurred in 2% versus 3% of patients in the chemoimmunotherapy and chemotherapy only groups, respectively. The authors concluded that the addition of rituximab improves PFS and OS in patients with previously untreated CLL.

In 2008, Tam et al reported the results of a Phase II study of 300 patients with previously untreated CLL who received a combination of fludarabine, cyclophosphamide, and rituximab (FCR), with a median follow-up of six years. Overall response rate was 95%, with a CR of 72%. Six-year OS was 77% and FFS was 51%. Compared to historical controls treated at the same institution with frontline fludarabine-based regimens, therapy with FCR was associated with a significantly superior OS (p<0.001); after adjusting for differences in pretreatment variables, FCR therapy emerged as the strongest independent predictor of survival (p<0.001, HR: 0.48). To date, the FCR regimen in this study has shown the highest CR rate, longest remission duration, and most favorable survival outcome for first-line therapy of CLL.

Byrd et al performed a retrospective comparison of the outcomes of patients enrolled in a randomized Phase II study of 104 previously untreated CLL patients who received sequential or concurrent fludarabine plus rituximab therapy to patients with similar pretreatment characteristics treated on the fludarabine arm (n=178) of a randomized Phase III trial comparing fludarabine, chlorambucil, or both. Results showed that patients who received fludarabine plus rituximab had a significantly better PFS and OS over the patients who received fludarabine alone. Two-year PFS probability was 0.67 (95% CI: 0.58–0.76) in patients who received fludarabine plus rituximab compared to 0.45 (95% CI: 0.37–0.52) for fludarabine alone (p<0.0001). Patients who received fludarabine plus rituximab had a two-year OS probability of 0.93 (95% CI: 0.88–0.98) versus 0.81 (95% CI: 0.75–0.87) with fludarabine alone (p=0.003).

Relapsed or Refractory CLL

The randomized, open-label multicenter Phase 3 REACH trial (2011) examined the efficacy of adding rituximab to fludarabine (F) and cyclophosphamide (C) in patients with relapsed or refractory CLL. Patients were eligible if they had received one prior line of chemotherapy, were fludarabine sensitive, and had not received prior therapy with rituximab. Patients were randomized to receive FC plus rituximab (n=276) or FC only (n=276). The primary end point

was PFS, with a median follow-up of 25 months. Median PFS was significantly prolonged in the FC plus rituximab group versus the FC only group (30.6 months vs 20.6 months, respectively; HR=0.65; $p<0.001$). Overall response rate, CR, and duration of overall response (HR=0.69; 95% CI, 0.50 to 0.96) also were significantly higher in the FC plus rituximab group. Median time to new treatment also was significantly longer in patients receiving rituximab (not reached vs 34.3 months; HR=0.65; 95% CI, 0.49 to 0.86; $p<0.01$).

In 2011, Badoux et al reported the final analysis of an open-label Phase 2 trial of 284 patients with relapsed CLL treated with FC and rituximab. All of the patients included in the study had active, progressive CLL and included patients in second and subsequent relapse and those previously treated with rituximab or FC combination. Median patient age was 60 years and median number of prior treatments was two (range 1-10). The primary objective was to improve the CR rate compared with historic control patients treated with FC as salvage therapy (n=114). Secondary outcomes included OS and PFS, calculated from the first day of therapy. 280 patients were evaluable for a response to FCR. 30% achieved CR, 14% achieved nodular partial remission (nPR), defined as patients who are otherwise in CR but have lymphoid nodules identified in bone marrow, and 30% achieved PR, for an overall response rate of 74%. When analyzed by prior therapy, patients with three or fewer prior therapies had significantly higher CR or nPR rates compared with those who received four or more prior regimens (52% versus 4%, respectively; $p<0.0001$). The estimated median PFS was 20.9 months (95% CI 18.8-27.6 months) for the entire cohort. The estimated median PFS for patients achieving CR was 60 months compared with 38 months for patients achieving nPR ($p=0.076$) and 15 months for those achieving PR ($p<0.001$). The estimated median OS for all patients was 46.7 months (95% CI, 41.2-53.4 months) and 100 months for patients who achieved CR or nPR. Compared with the historical cohort, patients receiving FCR had longer PFS compared to those receiving FC (21 months versus 11 months, respectively; $p<0.001$) and longer OS (47 months versus 21 months, respectively; $p<0.001$). A subgroup analysis showed that the following patients had superior outcomes with FCR: those with up to three prior treatments, fludarabine-sensitive patients regardless of prior rituximab exposure, and patients without chromosome 17 abnormalities.

Marginal Zone Lymphoma

Treatment with single agent rituximab can result in a reduction of splenomegaly and normalization of absolute lymphocyte counts in more than 90 percent of patients. A single institution retrospective analysis of 70 patients with splenic MZL, 43 of whom underwent treatment with rituximab alone (26 patients), chemotherapy alone (11 patients), or rituximab plus chemotherapy (six patients), reported excellent outcomes in patients treated with single agent rituximab. When compared with those who received chemotherapy alone, patients who received single agent rituximab had superior rates of overall response (88 versus 55 percent), three year survival (86 versus 45 percent), and three-year, failure-free survival (86 versus 45 percent). Outcomes in patients who received both rituximab and chemotherapy were similar to those seen for patients who received rituximab alone. Although this retrospective, uncontrolled study provides exciting initial data on the use of rituximab in this population, caution must be used in comparing treatment options based upon data generated in a nonrandomized fashion.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

NCCN guidelines (version 2. 2014) recommend rituximab for the following indications:

- FL (Grade 1 or 2): as first-line therapy as chemoimmunotherapy with bendamustine or CVP or CHOP (category 1); with fludarabine-based therapy (category 2B); or as single agent therapy (category 2A)
- FL (Grade 1 or 2): as first-line therapy as a single agent for elderly or infirm, if not able to tolerate above first-line therapy, (preferred) (category 2A) or with single agent alkylators (2A)
- FL (Grade 1 or 2): as maintenance therapy, first and second line (category 1)
- FL: second-line and subsequent therapy: with fludarabine-based therapy [fludarabine, cyclophosphamide, mitoxantrone, rituximab] (category 1); radioimmunotherapy (category 1); chemoimmunotherapy as in first-line treatment;
- Extranodal marginal zone B-cell lymphoma
- First-line therapy in DLBCL in combination with various chemotherapy regimens
- DLBCL as second-line therapy (in patients who are not candidates for hematopoietic stem-cell transplant) in combination with chemotherapy or as monotherapy
- CLL: in patients without del (11q) or del (17p)
 - First-line therapy: as single agent in frail patients with significant comorbidities (not able to tolerate purine analogs), in patients 70 years or older or younger patients with co-morbidities as single or combination therapy, and in patients younger than 70 years without significant comorbidities as combination therapy (all category 2A)
 - Relapsed/refractory: same as first-line therapy if long response (>3 years) until short response, and for short response (<2 years) in patients 70 years and older as single (category 2B) or combination (category 2A) and in patients younger than 70 years without significant comorbidities as combination therapy (category 2A)
- CLL: in patients with del (17p)
 - As combination therapy for first-line and relapsed/refractory disease (category 2A)
- CLL: in patients with del (11q):
 - First-line therapy age 70 years or older or younger patients with comorbidities as single agent or in combination (2A) and in patients age 70 years or less or older patients without significant comorbidities as combination therapy.
- CLL: in patients with del (11q):
 - As therapy for relapsed/refractory disease: same as first-line therapy if long response until short response; as single agent or in combination if short response for age 70 or greater; as combination therapy if short response for age less than 70 years or in older patients without significant comorbidities.
- Stage 1-2 nongastric mucosa-associated lymphatic tissue (MALT) in selected cases (category 2A).
- MCL as first- and second-line therapy in combination with chemotherapy (category 2A), and as maintenance therapy (category 1).
- As part of induction therapy and second-line therapy for Burkitt lymphoma
- In certain cases of lymphoblastic lymphoma, AIDS-related B-cell lymphoma, cutaneous B-cell lymphoma, post-transplant lymphoproliferative disorder and hairy cell leukemia.

Ofatumumab (Arzerra®)

A 2010 review article summarizes the clinical experience with ofatumumab.

Previously Untreated CLL

FDA-approval of ofatumumab for previously untreated CLL was based on one open-label, Phase 3 RCT, COMPLEMENT 1 (NCT00748189), which is currently unpublished. Information about COMPLEMENT 1 was obtained from the FDA-approved product label.

COMPLEMENT 1 enrolled 447 patients with previously untreated CLL who were considered by the investigator to be unsuitable for fludarabine-based chemotherapy, e.g., due to advanced age or comorbidities; 72% of patients had two or more comorbidities. Patients were randomized to receive ofatumumab (300 mg and 1000 mg intravenously [IV] on days one and eight of cycle 1, then 1000 mg on day one of each cycle) plus chlorambucil (10 mg/m² orally daily for the first seven days of each cycle) or chlorambucil alone for at least three 28-day cycles and at most 12 cycles (three cycles after maximal response). Sixty percent of patients received three to six cycles of ofatumumab, and 30% received seven to 12 cycles. PFS by blinded independent review (the primary end point) was 22 months in the ofatumumab group and 13 months in the chlorambucil monotherapy group (HR=0.57; 95% CI, 0.45 to 0.72). The most common Grade 3 or higher adverse reactions in the ofatumumab group were infusion reactions (10%) and neutropenia (26% vs 14% chlorambucil).

Relapsed or Refractory CLL

In a 2008 phase 1/2 open-label, dose-escalating trial, patients with relapsed or refractory CLL (N=33) were given weekly treatments of ofatumumab monotherapy. Patients had received a median of three previous treatments (range, 1-9). The objective response rate with the highest dose of ofatumumab was 50%, with most responses sustained at week 19. Most patients who received the highest dose had a greater than 50% decrease in lymph node size, which was sustained through 15 to 27 weeks. Median time to next CLL therapy was 12 months, and ofatumumab was well-tolerated. These initial, encouraging results with ofatumumab monotherapy in advanced CLL were further investigated in the multicenter study outlined next.

In 2010, Wierda et al reported a planned interim analysis of patients treated with ofatumumab monotherapy who had either fludarabine or alemtuzumab refractory (FA-ref) CLL or were ineligible for alemtuzumab treatment due to fludarabine-refractory CLL with bulky (>5 cm) lymphadenopathy (BF-ref). (These groups have poor outcomes with available salvage regimens: For comparison, the authors cited a case series of 99 patients with FA-ref CLL [n=58] or BF-ref [n=41] who were treated with a variety of salvage regimens, such as monoclonal antibodies, single agent or combination chemotherapy, or allogeneic hematopoietic stem-cell transplantation. Patients had low response rates [23% overall], short time-to-treatment failure [median, 2-3 months], and OS of 9 months).(49) Overall response rates (primary end point) were 58% (99% CI, 40 to 74) and 47% (99% CI, 32 to 62) in the FA-ref and BF-ref groups, respectively. Complete resolution of constitutional symptoms and improved performance status occurred in 57% and 48% of patients, respectively. In the FA-ref group, median PFS and OS were 5.7 months (95% CI, 4.5 to 8.0) and 13.7 months (95% CI, 9.4 to not reached), respectively, and 5.9 months (95% CI, 4.9 to 6.4) and 15.4 months (95% CI, 10.2 to 20.2) in the

BF-ref group, respectively. Adverse events were most commonly seen during treatment and included infusion reactions and infections and were primarily Grade 1 or 2 events.

FL

Czuczman and colleagues reported on the use of ofatumumab as monotherapy in rituximab-refractory FL. The median age of these patients was 61 years-old, and 47% had high-risk Follicular Lymphoma International Prognostic Index scores. Sixty-five percent were chemotherapy-refractory, and the median number of prior therapies was four. Overall response rate was 13% and 10% for two different doses, respectively. Among 27 patients refractory to rituximab monotherapy, overall response rate was 22%. Median PFS was 5.8 months. Grade 3-4 neutropenia, leukopenia, anemia, and thrombocytopenia occurred in a subset of patients. The authors concluded that ofatumumab was well tolerated and modestly active in this heavily pre-treated rituximab-refractory patient population.

Diffuse Large B-Cell Lymphoma

Two single-arm studies have examined ofatumumab for DLBCL. Coiffier et al (2013) administered weekly doses of ofatumumab (300 mg for the first dose followed by seven 1000 mg doses) to 81 patients with DLBCL who were transplant ineligible (n=56) or had relapsed/progressed after transplant (n=25). Patients had received a median of three (range, 1-7) previous treatments, and 95% had received previous rituximab. Fifty-eight percent of patients received all planned ofatumumab infusions, and median follow-up was 2.6 months. Overall response rate was 11% (2% CR, 9% PR), median duration of response was 9.5 months, and median PFS was 2.6 months. Neutropenia was the most common Grade 3 to 4 adverse event (11%). Grade 3 to 4 infusion reactions occurred in 5% of patients, and infections in 6%.

Matasar et al (2013) administered three 21-day cycles of ofatumumab in combination with ifosfamide, carboplatin, and etoposide or dexamethasone, cytarabine, and cisplatin to 61 transplant-eligible patients with relapsed or primary refractory, aggressive NHL (77% DLBCL, 20% transformed FL, 3% grade 3B FL). All patients received rituximab-containing primary treatment regimens. Ofatumumab was administered on days one and eight of cycle 1 (initially, 300 mg and 1000 mg, respectively; increased to 1000 mg for both doses based on safety data), and on day one of cycles 2 and 3 (1000 mg each). All patients completed treatment. For 59 CD20-positive patients, overall response rate was 61% (37% CR, 24% PR). Seventy-four percent of patients underwent stem-cell mobilization, and 56% underwent stem-cell transplant.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network Guidelines

NCCN guidelines (version 2.2014) recommend ofatumumab for the following indications (all category 2A):

As monotherapy in patients with relapsed or refractory CLL only:

- In patients without del (11q) or del (17p) who have a short response to initial therapy (<2 years): for age ≥ 70 years, age <70 years, or older patients without significant co-morbidities
- In patients with del (17p) with lymph nodes ≤ 5 cm
- In patients with del (11q), who have a short response to initial therapy (<2 years): for age ≥ 70 years, for age <70 years, or for older patients without significant co-morbidities

Obinutuzumab (Gazyva™)

Previously Untreated CLL

FDA-approval of obinutuzumab (also known as GA101) was based on one open-label, Phase 3 RCT, CLL11. CLL11 was conducted at 155 centers in 24 countries. Adults (>18 years of age) with previously untreated, CD20-positive CLL with coexisting medical conditions (eg, creatinine clearance 70-30 mL/min) were enrolled. Patients were randomized (2:2:1) to receive obinutuzumab (1000 mg IV weekly for three doses in cycle 1 then every 28 days for five additional cycles) plus chlorambucil (0.5 mg/kg orally every 14 days for six cycles; n=238), rituximab plus chlorambucil (n=233), or chlorambucil monotherapy (n=118). NCCN does not currently recommend chlorambucil monotherapy for first-line treatment of CLL. The primary end point was PFS. Only results comparing obinutuzumab combination therapy with chlorambucil monotherapy were considered by FDA for approval. Median follow-up was 14.2 months. Eighty-one percent of patients in the obinutuzumab group and 67% in the chlorambucil monotherapy group received all six treatment cycles. Median PFS by independent review was 23 months in the obinutuzumab group and 11 months in the chlorambucil group (HR=0.16; 95% CI, 0.11 to 0.24; p<0.001). Investigator-assessed PFS was similar. OS was increased in the obinutuzumab group compared with the chlorambucil group (HR for death, 0.41; 95% CI, 0.23 to 0.74; p=0.002), but OS data were not yet mature (medians had not been reached). In the rituximab group, median PFS by independent review was 16 months (HR vs chlorambucil monotherapy, 0.46; 95% CI, 0.35 to 0.61; p<0.001). Investigators compared PFS and OS in the obinutuzumab and rituximab groups. For PFS, HR for obinutuzumab was 0.39 (95% CI, 0.31 to 0.49; p<0.001). For OS, HR for obinutuzumab was 0.66 (95% CI, 0.41 to 1.06; p=0.08). Secondary end points included best overall response (CR plus PR; 77% obinutuzumab vs 31% chlorambucil; 66% rituximab), CR (29% vs 1% chlorambucil; 7% rituximab), and median duration of response (15 vs 4 months; not reported for rituximab). Statistical comparison of survival outcomes used stratified (by Binet stage and country/region) log-rank tests. Statistical comparison of response outcomes was not reported due to lack of adjustment for multiple comparisons.

The most common serious adverse event in CLL11 was infusion reaction (11%). Infusion reactions occurred in 69% of patients after the first dose of obinutuzumab, 3% after the second dose, and less than 1% thereafter. Premedication before the first infusion with IV corticosteroid, acetaminophen, and antihistamine became mandatory during the trial and is recommended in the product label. Late in the trial, the first dose of obinutuzumab in cycle 1 was divided over two days (100 mg on day 1 and 900 mg on day two). Incidence of Grade 3 to 4 neutropenia was 34% with obinutuzumab and 16% with chlorambucil; 32% of patients in the obinutuzumab group and 14% in the chlorambucil group received granulocyte colony-stimulating factor (G-CSF), which was administered per investigator discretion/institutional guidelines. Incidence of infections was similar between groups.

Relapsed or Refractory NHL

Obinutuzumab has been studied in Phase 1 and Phase 2 studies as monotherapy and in combination regimens for treatment of relapsed or refractory NHL. Dosage regimens differed from the current FDA-approved dose.

In a Phase 1 study, Radford et al (2013) enrolled 56 patients with CD20-positive relapsed/refractory FL who had received at most two previous chemotherapy or chemoimmunotherapy regimens. Patients received obinutuzumab with either CHOP (n=28) or fludarabine and cyclophosphamide (FC; n=28). Obinutuzumab was administered on days one and eight of cycle 1 and on day one in subsequent cycles. Within each chemotherapy group, patients were randomized 1:1 to receive either obinutuzumab 400 mg IV for all doses, or 1600 mg for the cycle 1 doses followed by 800 mg on day one of subsequent cycles (total 6-8 cycles with CHOP or 4-6 cycles with FC). At the end of induction, response rates were 96% (39% CR, 57% PR) in the CHOP group and 93% (50% CR, 43% PR) in the FC group.

In 2013, Salles et al and Morschhauser et al published results of the Phase 2 GAUGIN study of monotherapy with obinutuzumab, dosed as in the Phase 1 study for eight cycles. Salles et al enrolled 40 patients with relapsed/refractory indolent NHL (85% FL). At the end of treatment, response rates were 55% in the higher-dose group (9% CR, 46% PR) and 17% in the lower-dose group (all PR). Morschhauser et al enrolled 40 patients with relapsed/refractory aggressive NHL (63% DLBCL, 37% mantle cell lymphoma). At the end of treatment, response rates were 32% in the higher-dose group (all PR) and 24% in the lower dose group (10% CR, 5% unconfirmed CR, 10% PR).

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

NCCN guidelines (version 2.2014) recommend obinutuzumab for the following indications (all category 2A):

First-line therapy in combination with chlorambucil:

- In patients with CLL without del (11q) or del (17p): for frail patients with significant comorbidities (unable to tolerate purine analogs), for patients ≥70 years or younger patients with comorbidities, and for patients <70 years or older patients without significant co-morbidities
- In patients with CLL with del (17p)
- In patients with CLL with del (11q): for patients ≥70 years or younger patients with comorbidities, and for patients <70 years or older patients without significant co-morbidities

Alemtuzumab (Campath[®])

Patients with CLL and the presence of del (17p) (the location of the p53 gene) are generally resistant to chlorambucil, fludarabine, and rituximab, and patients with this mutation show disease progression and poor survival outcomes. Whereas median OS for patients with CLL is approximately 10 years, patients with del (17p) have a median survival of 32 months.

Alemtuzumab has been investigated as a treatment option in these patients.

Monotherapy

Alemtuzumab was initially approved in 2001 based on the pivotal CAM 211 Phase 3 study, in which 93 patients with relapsed or refractory CLL who had failed prior therapy with fludarabine or an alkylating agent, were treated with alemtuzumab, and significant responses were observed. Overall response rate was 33% (2% CR and 31% PR). Median time-to-progression was 4.7 months; median OS was 16 months (95% CI, 11.8 to 21.9) and 32 months for responders.

In a 2009 Phase 2 study, 103 patients with fludarabine-refractory CLL received at least one dose of alemtuzumab, and achieved an overall response rate of 34% (4% CR and 30% PR). Median PFS was 7.7 months, and median OS, 19.1 months.

Lozanski et al (2004) reported the effectiveness of alemtuzumab in 36 patients with fludarabine-refractory CLL, 15 (42%) of whom had p53 mutations or deletions. They observed a clinical response (complete or partial response) in six (40%) of 15 patients with this mutation versus a response rate of 19% in patients without.

In 2007, Hillmen et al reported on the CAM307 trial, which randomized 297 patients with previously untreated CLL to either alemtuzumab (n=149; median age, 59 years; range, 35-86) or chlorambucil (n=148; median, age 60 years; range, 36-83) as first-line treatment. Overall median PFS was 14.6 months (95% CI, 12.3 to 21.7 months) for patients in the alemtuzumab arm versus 11.7 months (95% CI, 9.9 to 13.2 months) in the chlorambucil arm (p=0.001). Overall and complete response rates were better in the alemtuzumab arm (83.2% vs 55.4%, p<0.001; 24.2% vs 2.0%; p<0.001, respectively). After a median follow-up of 24.6 months, 84% of patients in each arm were alive. Based on this study, FDA granted regular approval and expanded labeling for alemtuzumab as single-agent treatment for B-CLL. Commentary on the Hillmen et al trial raised several points: During the study's enrollment, work by Rai et al established an advantage of using fludarabine over chlorambucil as the basis of CLL therapy, with a shift toward fludarabine-based combination therapy in young patients. In addition, PFS in CAM307 was inferior to that observed in many randomized and Phase 3 studies published in the last decade, and CAM307 did not provide OS data past the median follow-up of 24.6 months.

In a single-arm study of 91 previously treated CLL patients, alemtuzumab led to eradication of minimal residual disease (MRD) in 20% of patients. Patients achieving an MRD-negative CR had longer median treatment-free survival (not reached) than MRD-positive CR patients (20 months) and MRD-positive PR patients (13 months; p<0.001). Five-year OS was 84% for MRD-negative patients, compared with approximately 10% for fludarabine-refractory patients treated with conventional salvage therapy. The authors concluded that MRD-negative remissions can be attained with alemtuzumab in patients with relapsed/refractory CLL, leading to improved OS and treatment-free survival.

A 2006 review article by Dearden summarized recent studies with single-agent alemtuzumab in the management of T-cell leukemia/lymphoma. One study of 39 patients with relapsed/refractory T-prolymphocytic leukemia (T-PLL) showed a 60% CR rate in patients treated with alemtuzumab, compared with a 9% CR rate with the purine nucleoside analog, 2-deoxycoformycin (DCF). Preliminary results in a study of 11 patients with treatment-naive T-PLL showed a CR rate of 100%. Despite these reported improved response rates, studies of the use of alemtuzumab in these disorders have been small and have not shown OS benefit. Further, some have been associated with significant toxicity and therefore require further investigation.

In Combination Chemoimmunotherapy

Elter and colleagues reported the results of a Phase 3, open-label, randomized trial in which fludarabine plus alemtuzumab was compared to fludarabine alone in patients with previously

treated (relapsed or refractory) CLL. The primary endpoint was PFS. Fludarabine plus alemtuzumab (n=168) resulted in better PFS than fludarabine monotherapy (n=167) (median 23.7 months [95% CI: 19.2-28.4] vs. 16.5 months [12.5-21.2]; hazard ratio (HR): 0.61 [95% CI: 0.47-0.80]; p=0.0003) and OS (median not reached vs. 52.9 months [40.9-not reached]; 0.65 [0.45-0.94]; p=0.021). Deaths due to adverse events were similar between the two groups.

Badoux and colleagues reported outcomes for 80 patients with relapsed or refractory CLL who were enrolled in a Phase 2 study and received alemtuzumab in addition to cyclophosphamide, fludarabine and rituximab. Patients were considered to be high-risk (e.g., refractory to fludarabine or high-risk cytogenetic abnormalities). Compared to historic controls, there was no significant improvement in PFS, and OS appeared worse.

Parikh and colleagues reported the results of a Phase 2 trial for 60 high-risk, previously untreated patients with CLL treated with fludarabine, cyclophosphamide, alemtuzumab and rituximab. High-risk was defined as serum β -2 microglobulin greater than or equal to 4mg/L. Response rates and survival were comparable to historic high-risk patients treated with fludarabine, cyclophosphamide, and rituximab.

In a Phase 3 RCT, Geisler et al (2014) randomized 272 patients with previously untreated, high-risk CLL to six 28-day cycles of daily oral fludarabine plus cyclophosphamide (FC) or FC plus subcutaneous alemtuzumab 30 mg on day one. High risk was defined as unmutated immunoglobulin heavy chain genes, deletion 17p or 11q, or trisomy 12. Three-year PFS (the primary end point) was increased in patients who received alemtuzumab (53% vs 37%; log-rank test, p=0.009). Among secondary end points: Overall survival was similar between groups (log-rank test, p=0.28); overall response rate was increased with alemtuzumab (88% vs 78%, p=0.036); and bone marrow minimal residual disease-negative CR was increased with alemtuzumab (64% vs 43%, p=0.016). Grade 3 or higher adverse events (62% vs 38%), and opportunistic infections (21% vs 8%) were more common with alemtuzumab, but treatment-related mortality was not (3.8% vs 4.3%).

Mauro et al (2014) administered first-line fludarabine and alemtuzumab to 45 young (age, <60 years) patients who had CLL with high risk cytogenetic abnormalities. Patients received four monthly courses of fludarabine 30 mg/m² IV plus alemtuzumab 30 mg IV on days one to three. Eighty-nine percent of patients completed treatment. Overall response rate was 76% (24% CR, 51% PR). Thirty-eight percent of patients developed Grade 3-4 granulocytopenia, and 13% developed severe infection. Two patients (4%) experienced Grade 3-4 infusion reaction.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

NCCN guidelines (version 2.2014) recommend alemtuzumab for the following indications (all category 2A):

- In the treatment of relapsed/refractory CLL in patients without del (11q) or (17p), in patients with a short response to first-line therapy (<2 years) and age \geq 70 with or without rituximab, and in patients with a short response to first-line therapy (<2 years) and age <70 or older patients without significant co-morbidities with fludarabine or with or without rituximab.

- In patients with CLL and del (17p) as first-line therapy (monotherapy or with rituximab) and for relapsed/refractory disease as combination therapy with chemotherapy, or with or without rituximab.
- In patients with CLL and del (11q) as relapsed/refractory therapy in patients with a short response (<2 years) to first-line therapy for age ≥ 70 years with or without rituximab and for patients with a short response (<2 years) for age <70 years or older patients without significant co-morbidities with fludarabine or with or without rituximab.
- for noncutaneous, peripheral T-cell lymphomas as second-line therapy in non-candidates for hematopoietic stem-cell transplantation.
- for cutaneous T-cell lymphomas (i.e., mycosis fungoides/Sézary syndrome) for refractory or progressive disease, Stage 3 or 4 (Sézary syndrome).
- for T-cell large granular lymphocytic leukemia in patients with primary refractory or relapsed/progressive disease.
- for T-cell prolymphocytic leukemia as primary treatment for symptomatic disease as monotherapy or in combination; intravenous is preferred to subcutaneous dosing.

Gemtuzumab Ozogamicin (Mylotarg[®])

FDA approval of gemtuzumab for patients with CD33-positive AML in first relapse who are aged 60 years or older and not candidates for other cytotoxic chemotherapies was based on an evaluation of 277 patients in three single-arm, open-label, Phase II studies. In two of the studies, patients were 18 years of age or older with a first remission duration of at least six months, and in the third study, only patients 60 years of age or older and in a first remission lasting at least three months were enrolled. Of the three studies combined, 157 patients were 60 years of age or older. The primary endpoint of the three studies was CR, and secondarily, CR that includes platelet transfusion independence (CRp). For the three pooled studies, in patients older than 60 years of age, the CR was 12%, and CRp was 12% (CR and CRp in patients younger than age 60 years were 13% and 14%, respectively). For patients who were younger than 60 years of age versus all 277 patients combined, the overall response rates were 28% and 26%, respectively. For patients 60 years of age or older, overall response rate was 24%. For those patients who completed the treatment period, median OS was 12.2 months for patients with CR and 12.9 months for patients in the CRp group (vs. 4.2 months for patients who did not enter remission; $p < 0.001$). The median OS for patients younger than age 60 years in the CR and CRp groups was 17.2 and 18.4 months, respectively. For patients 60 years of age or older, OS was 11.7; it was 11.4 months for those in the CR and CRp groups, respectively.

Lowenberg et al reported the results of a multicenter Phase III study randomizing patients older than 60 years of age with AML, or refractory anemia with excess blasts to three cycles of gemtuzumab or no post-remission therapy (control) after first CR was attained after intensive induction chemotherapy. The two treatment groups (113 received gemtuzumab and 119 were control patients) were comparable as regards to age (60–78 years, median: 67 years), performance status, and genetics. Sixty-five of the 113 patients completed the three cycles of gemtuzumab (a total of 110 of 113 received at least one cycle). The authors found no significant differences between treatment groups with regard to relapse probabilities, non-relapse mortality, DFS or OS, and concluded that post-remission treatment with gemtuzumab in older AML patients does not provide clinical benefit.

Burnett et al reported on the outcomes of an open-label trial of 1,113 patients, predominantly younger than 60 years of age, with previously untreated AML. Patients were randomized to the addition of gemtuzumab to induction and/or consolidation chemotherapy. The primary endpoints of the trial were response rate and survival. The addition of gemtuzumab was well-tolerated with no significant increase in toxicity. Overall, there was no difference with the addition of gemtuzumab in response or survival in either induction or consolidation. A predefined analysis by cytogenetics showed highly significant interaction with induction gemtuzumab (p=0.001) with significant survival benefit for patients with favorable cytogenetics, no benefit for patients with poor-risk disease, and a trend for benefit in intermediate-risk patients. The authors concluded that a substantial proportion of younger patients with AML have improved survival with the addition of gemtuzumab to induction chemotherapy with little additional toxicity.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

NCCN guidelines (version 2.2014) state that gemtuzumab is no longer commercially available in the U.S. after FDA withdrew its prior approval for the drug for the treatment of older patients with relapsed AML. However, trials suggested that the addition of gemtuzumab to standard induction regimens reduced the risk of relapse and improved OS outcomes in older patients with previously untreated AML. NCCN makes no recommendations on the use of gemtuzumab.

Summary

Rituximab

- Randomized studies have shown that the addition of rituximab to front-line chemotherapy has resulted in improved response rates and survival in follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL).
- The efficacy of rituximab as monotherapy in relapsed/refractory FL has been shown in noncomparative, multicenter trials.
- Randomized trials have shown improved progression-free survival (PFS) and overall survival (OS) with the use of rituximab as maintenance therapy, both in patients with previously untreated and previously treated FL.
- Randomized studies have shown that the addition of rituximab to chemotherapy has resulted in improved response rates and time-to-treatment failure in newly diagnosed mantle-cell lymphoma (MCL) and improved OS in relapsed or refractory disease.
- Randomized studies have shown improved PFS and OS with the addition of rituximab to chemotherapy in previously untreated chronic lymphocytic leukemia (CLL). One randomized study showed prolonged PFS in relapsed/refractory CLL, and a phase 2 open-label trial showed improved PFS and OS.
- Evidence for use of rituximab chemoimmunotherapy regimens for relapsed or refractory DLBCL comprises small, single-arm studies. Randomized studies are needed to assess net health benefits.

Ofatumumab

- Compared with historical controls, ofatumumab has shown improved OS rates in patients with CLL that is refractory to fludarabine and alemtuzumab or who are ineligible for alemtuzumab due to bulky disease.

- A Phase 3, randomized trial studied ofatumumab in patients with previously untreated CLL who had comorbidities and were not suitable for treatment with fludarabine. PFS was improved in patients who received ofatumumab plus chlorambucil compared with chlorambucil alone.
- More data are needed on the use of ofatumumab for rituximab-refractory FL and for aggressive NHL.

Obinutuzumab

- A Phase 3, randomized trial showed substantially improved PFS in patients with previously untreated CLL who received obinutuzumab compared with those who received chlorambucil or rituximab plus chlorambucil. Preliminary analysis of OS showed increased survival with obinutuzumab compared with chlorambucil monotherapy, but not compare with rituximab combination therapy.
- Small Phase 1 and 2 studies compared two doses of obinutuzumab in relapsed/refractory indolent and aggressive NHL, as monotherapy and in combination regimens. More data are needed to establish efficacy and safety of obinutuzumab for relapsed/refractory disease.

Alemtuzumab

- Single-agent alemtuzumab has shown efficacy in patients with CLL, particularly in the subgroup of patients with high-risk cytogenetic markers (eg, del[17p13.1]).
- More data are needed on the use of alemtuzumab as part of combination chemoimmunotherapy in the treatment of previously untreated and relapsed/refractory CLL.
- Small studies have shown some activity with alemtuzumab in relapsed/refractory cutaneous and peripheral T-cell lymphomas but also significant toxicity. A survival benefit has not been shown.

Gemtuzumab

On June 21, 2010, in agreement with FDA, Pfizer discontinued marketing Mylotarg® due to a lack of evidence to confirm clinical benefit of gemtuzumab as part of acute myeloid leukemia induction or maintenance therapy. Patients currently receiving gemtuzumab may complete their planned course of therapy; however, the drug is not commercially available to new patients.

U.S. Preventive Services Task Force

The use of monoclonal antibodies for the treatment of NHL and AML is not a preventive service.

Key Words:

Campath, Monoclonal Antibodies, B-Cell Malignancies, Mylotarg, Rituxan, alemtuzumab, ofatumumab, rituximab, Gemtuzumab ozogamicin, Leukemia, Lymphoma, Myeloid leukemia, Arzerra®, obinutuzumab, Gazyva

Approved by Governing Bodies:

Rituximab (Rituxan®, Pfizer) was initially approved by the U.S. Food and Drug Administration (FDA) on November 26, 1997, for the treatment of relapsed or refractory low-grade or follicular, CD20-positive, B cell NHL. Since 1997, rituximab has gained additional oncologic and nononcologic indications. Current FDA-approved oncologic indications of rituximab include follicular NHL, diffuse large B-cell lymphoma (DLBCL), and CLL.

On October 26, 2009, FDA granted accelerated approval to ofatumumab (Arzerra®, GlaxoSmithKline) for treatment of patients with CLL refractory to fludarabine and alemtuzumab. Full approval was contingent on results of a Phase 3 trial “intended to verify the clinical benefit of ofatumumab through demonstration of a clinically meaningful effect on progression-free survival.” On April 17, 2014, FDA converted the accelerated approval to full approval and added the indication, “in combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate.”

Obinutuzumab (Gazyva™, Genentech) is the first Breakthrough Therapy-designated drug to receive FDA approval, which was granted on November 1, 2013. The approved indication is for treatment of patients with previously untreated CLL in combination with chlorambucil.

Alemtuzumab (Campath®, Genzyme) was initially FDA-approved on May 7, 2001, for the treatment of previously treated patients with B-CLL who have failed fludarabine therapy. In September 2007, FDA expanded the approved labeling for alemtuzumab to include its use in previously untreated patients with B-CLL. The current FDA-approved indication for alemtuzumab is as single agent for treatment of B-CLL.

On June 21, 2010, in agreement with FDA, Pfizer discontinued marketing gemtuzumab (Mylotarg®) due to a lack of evidence to confirm clinical benefit in induction or maintenance regimens for AML. There also were safety concerns, including a relatively high rate of fatal induction-phase toxicities and higher than expected incidence of veno-occlusive disease. Marketing withdrawal was based on failure of a postapproval trial to confirm clinical benefit of gemtuzumab (trial S0106 conducted by the Southwest Oncology Group). Patients currently receiving gemtuzumab may complete their planned course of therapy; however, the drug is not commercially available to new patients.

Benefit Application:

Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply.

FEP: Special benefit consideration may apply.

Current Coding:

HCPCS Codes:

J9010	Injection, Alemtuzumab, 10 mg
J9300	Injection, Gemtuzumab ozogamicin, 5 mg

J9302	Injection, Ofatumumab, 10 mg
J9310	Injection, Rituximab, 100 mg
J9999	<u>Not otherwise classified, antineoplastic drugs</u>

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Policy History:

Medical Policy Panel, May 2011

Medical Policy Group, June 2011 (2): New Policy

Medical Policy Administration Committee, June 2011

Available for comment June 23 – August 8, 2011

Medical Policy Group, August 2011: Added CPT code for Arzerra

Medical Policy Administration Committee, September 2011

Medical Policy Panel, May 2012

Medical Policy Group, July 2012 (2): Updated Key Points and References

Medical Policy Panel, July 2013

Medical Policy Group, September 2013 (2): Policy statement added that ofatumumab is considered investigational for the treatment of malignancies other than B-cell CLL. Key Points and References updated to support policy statement.

Medical Policy Administration, September 2013

Available for comment September 19 through November 2, 2013

Medical Policy Group, June 2014 (1): Policy statement added that ofatumumab is approved for coverage in combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate back dated to FDA approval date of 4/17/14; update to Governing Bodies in association with the new coverage; no other changes to policy statements

Medical Policy Administration Committee, June 2014

Available for comment June 10 through July 25, 2014

Medical Policy Panel, July 2014

Medical Policy Group, August 2014 (1): Update to Description, Policy, Key Points, Key Words, Governing Bodies, Coding and References related to addition of Gazyva criteria and adding all oncologic related criteria for rituximab from MP #044-Rituximab

Medical Policy Administration Committee, September 2014

Available for comment September 6 through October 20, 2014

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.