

## Evidence Based Guideline

# Monoclonal Antibodies for Non-Hodgkin Lymphoma, including Chronic Lymphocytic, & Acute Myeloid Leukemia In the Non-Hematopoietic Stem Cell Transplant Setting

<b>File Name:</b>	monoclonal_antibodies_for_non_hodgkin_lymphoma_acute_myeloid_leukemia
<b>Origination:</b>	7/2009
<b>Last CAP Review:</b>	4/2011
<b>Next CAP Review:</b>	4/2012
<b>Last Review:</b>	8/2011

### Description of Procedure or Service

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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).

Rituximab (Rituxan®) is a chimeric murine/human monoclonal antibody directed against the surface antigen CD20, which is expressed on all normal B lymphocytes and more than 90% of B-cell non-Hodgkin lymphomas (NHL). Rituximab induces lysis of B cells (normal and malignant) that express CD20, and also sensitizes B cells to the cytotoxic effect of chemotherapy.

Ofatumumab (Arzerra) is also a monoclonal antibody directed against CD20. It targets an epitope that differs from the binding location of rituximab. Rituximab complement-dependent cytotoxicity is dependent on CD20 expression; chronic lymphocytic leukemia (CLL) cells underexpress CD20, whereas ofatumumab does not appear to be similarly dependent on receptor intensity. 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, it 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 the 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, but not by pluripotent hematopoietic stem cells. Binding of the anti-CD33 antibody with the CD33 antigen results in formation of a complex that is internalized and eventually leads to DNA double-strand breaks and cell death.

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

**For non-oncologic uses of rituximab**, please see BCBSNC Corporate Medical Policy, Rituximab for the Treatment of Rheumatoid Arthritis.

### Regulatory status

On 1/28/2011, the U.S. Food and Drug Administration (FDA) approved a new expanded indication for rituximab for previously untreated follicular CD20-positive, B-cell NHL in combination with first-line

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chemotherapy and, in patients achieving a complete (CR) or partial response (PR) to Rituxan in combination with chemotherapy, as single-agent maintenance therapy.

On October 26, 2009, the U.S. Food and Drug Administration granted accelerated approval to ofatumumab (Arzerra, GlaxoSmithKline) for the treatment of patients with CLL refractory to fludarabine and alemtuzumab.

In September 2007, the FDA expanded the approved labeling for alemtuzumab to include its use in previously untreated patients with B-CLL (previous label approved only for treatment of B-CLL in treatment-experienced patients, specifically those who had been treated with an alkylating agent and whose disease was not adequately responding to fludarabine therapy).

On June 21, 2010, in agreement with the U.S. Food and Drug Administration (FDA), the commercial marketing of Mylotarg® was voluntarily discontinued due to a lack of evidence to confirm clinical benefit for gemtuzumab as part of induction or maintenance therapy of AML. In addition, there were safety concerns, including a relatively high rate of fatal induction phase toxicities and higher than expected incidence of veno-occlusive disease. The withdrawal was based on the failure of a postapproval trial to confirm clinical benefit for gemtuzumab (trial S0106 conducted by the Southwest Oncology Group). Patients who are currently receiving gemtuzumab may complete their planned course of therapy; however, the drug will not be commercially available to new patients.

**\*\*\*Note: This Evidence Based Guideline is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

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1. Rituximab (Rituxan®) may be appropriate to treat patients with B-cell non-Hodgkin lymphoma (NHL) in any of the following:
  - a. 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
  - b. when used with CHOP or other anthracycline-based chemotherapy as first-line treatment for patients with diffuse large B-cell lymphoma (DLBCL),\*
  - c. for recurrent, aggressive CD20-positive NHL,
  - d. for previously untreated or relapsed/refractory mantle cell lymphoma,
  - e. as combination therapy in previously untreated B-cell chronic lymphocytic leukemia (B-CLL).
2. Ofatumumab (Arzerra) may be appropriate for the treatment of CLL that is refractory to fludarabine and alemtuzumab.\*
3. Alemtuzumab (Campath®) may be appropriate as a single agent for the treatment of B-cell chronic lymphocytic leukemia (B-CLL)\* in patients with a chromosome deletion of 17p [del (117p)] or in patients not suitable for treatment with fludarabine.
4. Gemtuzumab ozogamicin (Mylotarg®) may be appropriate 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.

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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.

Rituximab is approved by the FDA for the following oncologic indications:

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent.
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first-line chemotherapy and, in patients achieving a complete or partial response to Rituxan in combination with chemotherapy, as single-agent maintenance therapy.
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cytomegalovirus (CVP) chemotherapy.
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or 31 other anthracycline-based chemotherapy regimens.
- In combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

Treatment of B-CLL with monoclonal antibody therapy is used in patients with non-localized disease (i.e., Ann Arbor, stage II-IV).

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

## Medical Evidence regarding Monoclonal Antibodies for Non-Hodgkin Lymphoma, including Chronic Lymphocytic Leukemia, and Acute Myeloid Leukemia indicates it is not recommended in the following situations

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1. For conditions other than those listed above.
2. Alemtuzumab (Campath®) is not recommended for the treatment of malignancies other than B-cell CLL.
3. Ofatumumab (Arzerra) is not recommended in previously untreated CLL or as maintenance therapy in patients with CLL.
4. Gemtuzumab ozogamicin (Mylotarg®) is not recommended for:
  - a. treatment of patients with AML and who are younger than 60 years of age,
  - b. treatment of newly diagnosed AML,
  - c. treatment of second or subsequent relapse of AML,
  - d. use in combination with cytotoxic chemotherapy.

## Benefits Application

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This evidence based guideline relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this guideline.

## Billing/Coding/Physician Documentation Information

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This guideline may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative

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Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: J9010, J9300, J9310*

## **Scientific Background and Reference Sources**

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BCBSA Medical Policy Reference Manual, 2.03.05, 5/14/09

Senior Medical Director 7/2009

Specialty Matched Consultant Advisory Panel – 5/2010

BCBSA Medical Policy Reference Manual, 2.03.05, 5/13/2010

Specialty Matched Consultant Advisory Panel – 4/2011

BCBSA Medical Policy Reference Manual. 2.03.05, 5/12/11

Medical Director – 8/2011

## **Policy Implementation/Update Information**

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9/28/09 New evidence based guideline. Reviewed with Senior Medical Director 7/20/09. (btw)

6/22/10 Policy Guideline Number(s) removed (amw)

7/6/2010 Specialty Matched Consultant Advisory Panel review 5/24/2010. No changes to Guideline. References added. (btw)

5/24/11 Specialty Matched Consultant Advisory Panel review 4/27/11. Updated “Description” section. Added the following statement to #3 in the “Evidence-Based Guideline” section; “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.” References added. (btw)

08/16/11 Updated “Description” section to include information related to Ofatumumab (Arzerra) and to update the Regulatory Status. Added the following statement to the “Evidence Based Guideline” section to indicate; “Rituxan may be appropriate a. 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.” and “Ofatumumab (Arzerra) may be appropriate for the treatment of CLL that is refractory to fludarabine and alemtuzumab.\*” Rituximab approved FDA indications added. “Ofatumumab (Arzerra) is not recommended in previously untreated CLL or as maintenance therapy in patients with CLL.” Added to the “Not Recommended” section. References added. Medical Director review 8/6/2011. (btw)

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