

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

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[POLICY RATIONALE](#)
[DISCLAIMER](#)
[POLICY HISTORY](#)

[PRODUCT VARIATIONS](#)
[DEFINITIONS](#)
[CODING INFORMATION](#)

[DESCRIPTION/BACKGROUND](#)
[BENEFIT VARIATIONS](#)
[REFERENCES](#)

I. POLICY

Note: Please refer to MP-2.110 Rituximab (Rituxan®) for treatment of cancer indications with the monoclonal antibody Rituximab (Rituxan®). Also, see cross-references for other monoclonal antibodies used to treat cancer indications.

Ofatumumab (Arzerra®)

Ofatumumab (Arzerra®) may be considered **medically necessary** for the following indications:

- In combination with chlorambucil, for the treatment of previously untreated patients with chronic lymphocytic leukemia (CLL) for whom fludarabine-based therapy is inappropriate; or
- For the treatment of chronic lymphocytic leukemia (CLL) that is refractory to fludarabine and alemtuzumab.*

Ofatumumab (Arzerra®) is considered **investigational** as maintenance therapy in patients with chronic lymphocytic leukemia (CLL).

Ofatumumab (Arzerra®) is considered **investigational** for the treatment of malignancies other than B-cell CLL.

Alemtuzumab (CamPath®)

Alemtuzumab (CamPath®) may be considered **medically necessary** 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®) is considered **investigational** for the treatment of malignancies other than B-cell CLL as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

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

Cross-reference:

- MP-2.104** Trastuzumab (Herceptin®)
- MP-2.110** Rituximab (Rituxan®)
- MP-2.128** Bevacizumab (Avastin®) for Cancer Indications
- MP-2.150** Cetuximab (Erbitux®)
- MP-2.157** Denosumab (Xgeva™)
- MP-2.161** Ipilimumab (Yervoy™)
- MP-5.022** Radioimmunosciintigraphy Imaging (Monoclonal Antibody Imaging) with Indium-111 Capromab Pendetide (Prostascint®) for Prostate Cancer
- MP-2.103** Off-Label Use of Prescription Drugs

II. PRODUCT VARIATIONS

[TOP](#)

[N] = No product variation, policy applies as stated

[Y] = Standard product coverage varies from application of this policy, see below

- | | |
|--------------------------|-----------------|
| [N] Capital Cares 4 Kids | [N] Indemnity |
| [N] PPO | [N] SpecialCare |
| [N] HMO | [N] POS |
| [N] SeniorBlue HMO | [Y] FEP PPO* |
| [N] SeniorBlue PPO | |

*Refer to FEP Medical Policy Manual MP-5.04.03 Arzerra and MP-5.04.05 Campath. The FEP Medical Policy manual can be found at:

www.fepblue.org

III. DESCRIPTION/BACKGROUND

[TOP](#)

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.

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

Ofatumumab (Arzerra) is 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 under express CD20, whereas ofatumumab does not appear to be similarly dependent on receptor intensity.

On April 17, 2014, the U. S. Food and Drug Administration approved ofatumumab (Arzerra Injection, for intravenous infusion; GlaxoSmithKline) in combination with chlorambucil, for the treatment of previously untreated patients with chronic lymphocytic leukemia (CLL), for whom fludarabine-based therapy is considered inappropriate.

Black Box Warning for Ofatumumab (Arzerra)

WARNING: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death.
- Progressive Multifocal Leukoencephalopathy (PML) resulting in death.

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, the antibody 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.

Black Box Warning for Alemtuzumab (Campath®)

WARNING: CYTOPENIAS, INFUSION REACTIONS, and INFECTIONS

- **Cytopenias:** Serious, including fatal, pancytopenia/marrow hypoplasia, autoimmune idiopathic thrombocytopenia, and autoimmune hemolytic anemia can occur in patients receiving Campath. Single doses of Campath greater than 30 mg or cumulative doses greater than 90 mg per week increase the incidence of pancytopenia.
- **Infusion Reactions:** Campath administration can result in serious, including fatal, infusion reactions. Carefully monitor patients during infusions and withhold Campath for Grade 3 or 4 infusion reactions. Gradually escalate Campath to the recommended dose at the initiation of therapy and after interruption of therapy for 7 or more days
- **Infections:** Serious, including fatal, bacterial, viral, fungal, and protozoan infections can occur in patients receiving Campath. Administer prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) and herpes virus infections.

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

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

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. (Mylotarg® is no longer commercially available to new patients, see regulatory status).

Regulatory status

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). Labeling indications for alemtuzumab are as monotherapy for the treatment of CLL.

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 (Mylotarg®) 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 post approval trial to confirm clinical benefit for gemtuzumab (trial S0106 conducted by the Southwest Oncology Group). Patients who are currently receiving gemtuzumab (Mylotarg®) may complete their planned course of therapy; however, the drug will not be commercially available to new patients.

IV. RATIONALE

[TOP](#)

Ofatumumab (Arzerra®)

A 2010 review article summarizes the clinical experience with ofatumumab. (1)

CLL

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

In 2008, in a Phase 1/2 open-label, dose-escalating trial, patients with relapsed or refractory CLL (n=33) were given weekly treatments of ofatumumab monotherapy. (39) Patients had received a median of 3 previous treatments (range, 1-9 treatments). The objective response rate with the highest dose of ofatumumab was 50%, with most responses sustained at week 19. The majority of patients who received the highest dose had a greater than 50% decrease in lymph node size, which was sustained through 15-27 weeks. The median time to next CLL therapy was 12 months, and the ofatumumab was well-tolerated. These initial, encouraging results with ofatumumab monotherapy in advanced CLL were further investigated in a multicenter study, (40) as outlined below.

In 2010, Wierda and colleagues 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). (40) (These groups have poor outcomes with available salvage regimens. For comparison, the authors cite 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, including 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 an OS of 9 months). (41) The overall response rates (primary endpoint) were 58% (99% CI: 40-74%) and 47% (99% CI: 32-62%) 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: 4.5-8.0) and 13.7 months (95% CI: 9.4-not yet reached), respectively, and 5.9 months (95% CI: 4.9-6.4) and 15.4 months (95% CI: 10.2-20.2) 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. (42) 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 4. Overall response rate was 13% and 10% for 2 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.

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

The authors concluded that ofatumumab was well tolerated and modestly active in this heavily pre-treated, rituximab-refractory patient population.

On April 17, 2014, the U. S. Food and Drug Administration approved ofatumumab (Arzerra Injection, for intravenous infusion; GlaxoSmithKline) in combination with chlorambucil, for the treatment of previously untreated patients with chronic lymphocytic leukemia (CLL), for whom fludarabine-based therapy is considered inappropriate.

The approval was based on the results of a multi-center, randomized, open-label trial comparing ofatumumab in combination with chlorambucil to single agent chlorambucil. The trial enrolled 447 patients for whom fludarabine-based therapy was considered to be inappropriate by the investigator for reasons that included advanced age or presence of co-morbidities. In the overall trial population the median age was 69 years (range: 35 to 92 years). Seventy-two percent of patients had two or more co-morbidities and 48% of patients had a creatinine clearance of <70 mL/min. Patients received ofatumumab as an intravenous infusion according to the following schedule: 300 mg administered on cycle 1 day 1, 1000 mg administered on cycle 1 day 8 and 1000 mg administered on day 1 of all subsequent 28 day cycles. In both arms, chlorambucil was given at a dose of 10 mg/m² orally on days 1 to 7 every 28 days. Prior to each infusion of ofatumumab, patients received pre-medication with acetaminophen, an antihistamine, and a glucocorticoid.

The primary endpoint of the trial was progression free survival (PFS) as assessed by a blinded Independent Review Committee (IRC) using the 2008 International Workshop on Chronic Lymphocytic Leukemia (IWCLL) update of the National Cancer Institute Working Group (NCI-WG) guidelines. Median PFS was 22.4 months (95% CI: 19.0, 25.2 months) for patients receiving Arzerra in combination with chlorambucil compared to 13.1 months (95% CI: 10.6, 13.8 months) for patients receiving single-agent chlorambucil [hazard ratio 0.57 (95% CI: 0.45, 0.72), stratified log-rank p-value <0.001].

National Comprehensive Cancer Network Guidelines

National Comprehensive Cancer Network (NCCN) guidelines (38) state that use of ofatumumab includes the following indications:

As monotherapy:

- In patients with CLL relapsed/refractory 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 (category 2A)

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

- In patients with CLL relapsed/refractory with del (17p) with lymph nodes <5 cm- (category 2A)
- In patients with CLL relapsed/refractory 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 (category 2A)

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)

A search of the National Cancer Institute’s Physician Data Query (PDQ) database identified 8 Phase III trials investigating the use of ofatumumab in the treatment of CLL, in patients who are previously untreated, as maintenance therapy and in the relapsed/refractory setting as monotherapy or combination therapy. (NCT00748189, NCT00824265, NCT01039376, NCT01077518, NCT01200589, NCT01313689, NCT00349349)

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

Monotherapy

Alemtuzumab was initially approved in 2001 after the results of 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. (44) The overall response rate was 33% (2% CR and 31% PR). Median time to progression was 4.7 months and median OS was 16 months (95% CI: 11.8-21.9) and 32 months for responders.

In a Phase 2 study, 103 patients with fludarabine-refractory CLL received at least 1 dose of alemtuzumab, and achieved an overall response rate of 34% (4% CR and 30% PR). (45) Median PFS was 7.7 months and median OS, 19.1 months.

Lozanski and colleagues reported the effectiveness of alemtuzumab in 36 patients with fludarabine-refractory CLL, 15 (42%) of whom had p53 mutations or deletions. (46) They

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

observed a clinical response (complete or partial response) in 6 of 15 (40%) patients with this mutation versus a response rate of only 19% in patients without.

In 2007, Hillmen and colleagues reported the results of the CAM307 trial, which randomized 297 patients with previously untreated CLL to either alemtuzumab (n=149; median age 59 years; range, 35–86 years) or chlorambucil (n=148; median age 60 years; range, 36–83 years) as first-line treatment. (47) Overall median PFS was 14.6 months (95% CI: 12.3–21.7 months) for patients in the alemtuzumab arm versus 11.7 months (95% CI: 9.9–13.2 months) in the chlorambucil arm (p=0.0001). Overall and complete response rates were better in the alemtuzumab arm, 83.2% versus 55.4% (p<0.0001) and 24.2% versus 2.0% (p<0.0001), respectively. After a median follow-up of 24.6 months, 84% of the patients in each arm were alive. Based on this study, the U.S. Food and Drug Administration (FDA) granted regular approval and expanded labeling for alemtuzumab as single-agent treatment for B-cell chronic lymphocytic leukemia (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 the use of fludarabine-based combination therapy in young patients. (48) In addition, the PFS shown in the CAM307 study was inferior to that observed in many randomized and Phase III studies published in the last decade, and the CAM307 trial did not provide OS data past the trial 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. (49) Patients achieving an MRD-negative complete response had longer treatment-free survival (not reached) than MRD-positive complete response patients (20 months) and MRD-positive partial response patients (13 months; p<0.0001). Five-year OS was 84% for the MRD-negative patients, compared to approximately 10% of fludarabine-refractory patients treated with conventional salvage therapy expected to survive 5 years. The authors conclude that MRD-negative remissions can be attained with alemtuzumab in patients with relapsed/refractory CLL, leading to improvement in OS and treatment-free survival.

A review article by Dearden summarizes recent studies with single-agent alemtuzumab in the management of T-cell leukemia/lymphoma. (50) One study of 39 patients with relapsed/refractory T-prolymphocytic leukemia (T-PLL) showed a 60% CR rate in patients treated with alemtuzumab, compared to a 9% CR rate with the purine nucleoside analog 2-deoxycoformycin (DCF). Preliminary results in a study of 11 patients with treatment-naïve T-PLL showed a CR rate of 100%. Despite these reported improved response rates, studies of

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

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.

As 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. (51) 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. (52) 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. (53) High risk was defined as serum β -2 microglobulin greater than or equal to 4 mg/L. Response rates and survival were comparable to historic high-risk patients treated with fludarabine, cyclophosphamide, and rituximab.

National Comprehensive Cancer Network (NCCN) Guidelines

NCCN guidelines (38) state that alemtuzumab is indicated (all category 2A):

- As first-line treatment of CLL in patients without del (11q) or del (17p), as monotherapy in patients 70 years of age or older.
- 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.

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

- 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 first-line therapy in patients age ≥ 70 years or younger patients with co-morbidities as monotherapy.
- 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/Sezary syndrome) for refractory or progressive disease, stage 3 or 4 (Sezary syndrome).
- for T-cell prolymphocytic leukemia as primary treatment for symptomatic disease as monotherapy or in combination.

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)

A search of the National Cancer Institute’s PDQ database identified 3 Phase III trials investigating the use of alemtuzumab in B-CLL, including as front-line therapy and in the relapsed/refractory setting. (NCT00046683, NCT00086580, NCT00564512)

One Phase III trial is ongoing investigating the value of alemtuzumab in previously untreated T-cell malignancies in the non-hematopoietic stem-cell transplant setting. NCT00725231 is an open-label interventional trial that will randomize elderly patients with previously untreated peripheral T-cell lymphoma to CHOP-14 with or without alemtuzumab. Estimated enrollment is 274, with an estimated study completion date of March 2014.

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 3 single-arm, open-label, Phase II studies. (54) In 2 of the studies, patients were 18 years of age or older with a first remission duration of at least 6 months, and in the third study, only patients 60 years of age or older and in a first remission

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

lasting at least 3 months were enrolled. Of the 3 studies combined, 157 patients were 60 years of age or older. The primary endpoint of the 3 studies was CR, and secondarily, CR that includes platelet transfusion independence (CRp). For the 3 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 and colleagues reported the results of a multicenter Phase III study randomizing patients older than 60 years of age with acute myeloid leukemia (AML), or refractory anemia with excess blasts to 3 cycles of gemtuzumab or no post-remission therapy (control) after first CR was attained after intensive induction chemotherapy. (55) The 2 treatment groups (113 received gemtuzumab and 119 were control patients) were comparable regarding age (60–78 years, median: 67 years), performance status, and genetics. Sixty-five of the 113 patients completed the 3 cycles of gemtuzumab (a total of 110 of 113 received at least 1 cycle). The authors found no significant differences between treatment groups with regard to relapse probabilities, nonrelapse mortality, disease-free survival (DFS) or OS, and concluded that post-remission treatment with gemtuzumab in older AML patients does not provide clinical benefit.

Burnett and colleagues reported on the outcomes of an open-label trial of 1,113 patients, predominantly younger than 60 years of age, with previously untreated AML. (56) 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

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

proportion of younger patients with AML have improved survival with the addition of gemtuzumab to induction chemotherapy with little additional toxicity.

NCCN Guidelines

NCCN guidelines (57) state that gemtuzumab is no longer commercially available in the U.S. after the U.S. Food and Drug Administration (FDA) withdrew its prior approval for the drug for the treatment of older patients with relapsed AML, but that trials suggest 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.

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)

A search of the National Cancer Institute’s Physician Data Query database identified 11 Phase II/III and Phase III trials to assess chemotherapy with or without gemtuzumab. Studies include patients in various age groups (including those younger than 60 years of age) and with relapsed and previously untreated AML: NCT00454480, NCT00085709, NCT00372593, NCT00492856, NCT00860639, NCT00893399, NCT00121303, NCT00927498, NCT00052299, NCT00091234 and NCT00049517.

Physician Specialty Society and Academic Medical Center Input

In response to requests, input was received from a physician specialty society and 2 academic medical centers while this policy was under review in 2009, for a total of 4 reviews. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. Two reviewers commented on 3 monoclonal antibodies addressed in the policy, and 2 only commented on gemtuzumab. (This policy was sent out for vetting before the addition of ofatumumab to the policy).

Rituximab: The 2 reviewers were split on the use of rituximab 1) with CHOP as first-line therapy for FL, 2) as first- and second-line therapy of MCL, and 3) in the treatment of relapsed or refractory CLL.

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

Alemtuzumab: Both reviewers agree with the policy statements and state that alemtuzumab is most appropriately used in patients with a chromosome 17p deletion, or any patient not suitable for treatment with fludarabine (1 reviewer).

Gemtuzumab: Three of the 4 reviewers agreed on the statement of medical necessity; 3 of the 4 reviewers disagreed with the investigational statement, and all 3 based this on the results of a recent, large Phase III study using gemtuzumab in patients predominantly younger than age 60 years; at the time of their review, this study was available in abstract form; it has since been published in its entirety. (51)

Summary

- Ofatumumab.

Compared to 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.

More data are needed on the use of ofatumumab in patients with rituximab-refractory FL.

- Alemtuzumab:

Single-agent alemtuzumab has shown efficacy in patients with CLL, particularly in the subgroup of patients with high-risk cytogenetic markers (e.g., 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 have been associated with significant toxicity, and not shown survival benefit.

- Gemtuzumab:

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. Patients who are currently receiving gemtuzumab may complete their planned course of therapy; however, the drug will not be commercially available to new patients.

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

V. DEFINITIONS

[TOP](#)

B-CELL is a lymphocyte (white blood cell) that matures in bone marrow and then migrates to lymphoid tissues, where a foreign antigen stimulates it to produce antibodies.

CLINICAL TRIAL is a carefully designed and executed investigation of the effects of a drug administered to human subjects. The goal is to define the clinical efficacy and pharmacological effects.

CYTOTOXIC refers to destruction of cells.

IMMUNOTHERAPY is the use of natural or synthetic substances to stimulate or suppress the immune response, to treat deficits or to interfere with the growth of malignant neoplasms.

OFF-LABEL refers to the use of a drug to treat a condition for which it has not been approved by the U.S. Food and Drug Administration (FDA), especially when such may relieve unpleasant symptoms or prove compassionate. Drug effects that have been observed but not specifically proven (and for which no application has been made) may be exploited for unproven, or "off-label" uses by licensed medical practitioners.

VI. BENEFIT VARIATIONS

[TOP](#)

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

VII. DISCLAIMER

[TOP](#)

Capital's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital considers the

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

[TOP](#)

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

HCPCS Code	Description
J9010	INJECTION, ALEMTUZUMAB, 10 MG
J9302	INJECTION, OFATUMUMAB, 10 MG

ICD-9-CM Diagnosis Code*	Description
204.10	CHRONIC LYMPHOID LEUKEMIA, WITHOUT MENTION OF HAVING ACHIEVED REMISSION
204.12	CHRONIC LYMPHOID LEUKEMIA, IN RELAPSE
205.00	ACUTE MYELOID LEUKEMIA, WITHOUT MENTION OF HAVING ACHIEVED REMISSION
205.02	ACUTE MYELOID LEUKEMIA, IN RELAPSE

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

The following ICD-10 diagnosis codes will be effective October 1, 2015:

ICD-10-CM Diagnosis Code*	Description
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
C92.00	Acute myeloblastic leukemia, not having achieved remission
C92.60	Acute myeloid leukemia with 11q23-abnormality not having achieved remission
C92.a0	Acute myeloid leukemia with multilineage dysplasia, not having achieved remission
C92.50	Acute myelomonocytic leukemia, not having achieved remission
C92.40	Acute promyelocytic leukemia, not having achieved remission

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

ICD-10-CM Diagnosis Code*	Description
C92.90	Myeloid leukemia, unspecified, not having achieved remission
C92.02	Acute myeloblastic leukemia, in relapse
C92.62	Acute myeloid leukemia with 11q23-abnormality in relapse
C92.a2	Acute myeloid leukemia with multilineage dysplasia, in relapse
C92.52	Acute myelomonocytic leukemia, in relapse
C92.42	Acute promyelocytic leukemia, in relapse

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

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[TOP](#)

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POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

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POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
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POLICY NUMBER	MP-2.139

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POLICY NUMBER	MP-2.139

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POLICY NUMBER	MP-2.139

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POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

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X. POLICY HISTORY

[TOP](#)

MP 2.110	CAC 10/29/02
	CAC 1/25/05
	CAC 2/28/06
	CAC 5/30/06
	CAC 10/31/06
	CAC 11/27/07
	CAC 1/27/09
MP-2.139	CAC 11/24/09 Policy revised - Rituximab criteria removed. New MP number assigned.
	CAC 9/28/10 Consensus review- information regarding Mylotarg (removed from the market 6/10) revised.
	CAC 11/22/11 Minor review. Added ofatumumab medically necessary and investigational indications. Added Black Box Warning for alemtuzumab. Revised policy title per BCBSA.
	CAC 2/28/2012 Adopted BCBSA. Revised investigational statement for alemtuzumab (Campath®) to match BCBSA.
	CAC 6/4/13 , Consensus list review. Administrative code review complete.
	CAC 3/25/14 Consensus. Policy statement added that ofatumumab is considered investigational for the treatment of malignancies other than B-cell CLL. References updated. Rationale section added.
	CAC 5/20/14 Minor revision. Policy being revised to add new FDA-approved indication for Ofatumumab (Arzerra) for use in combination with chorambucil, for the treatment of previously untreated patients with chronic lymphocytic leukemia (CLL) for whom fludabrine-based therapy is considered inappropriate. Reference and rationale update. Black box warning added for Arzerra. Codes reviewed.

POLICY TITLE	USES OF MONOCLONAL ANTIBODIES FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA IN THE NON-HEMATOPOIETIC STEM-CELL TRANSPLANT SETTING
POLICY NUMBER	MP-2.139

[Top](#)

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