

National Drug Monograph
Ofatumumab (Arzerra™)
September 2010, Updated August 2014
VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Outcome in clinically significant area	CLL Relapsed/Refractory (R/R): ORR CLL (previously untreated): PFS
Effect Size	CLL (R/R): ORR 58%, PFS 5.7 months, OS 13.7 months CLL (previously untreated): PFS 22 vs 13 months; HR 0.57 (0.45, 0.72); p< 0.001
Potential Harms	Neutropenia (all grades) 66%; (gr 3, 4) 42% Infections (all grades) 70%; (gr 3,4) 29% Infusion-related reactions w/first infusion: 38%
Net Clinical Benefit	CLL (R/R): Moderate CLL (previously untreated): Moderate

Definitions

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life

Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio

Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)

Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Executive Summary:

Ofatumumab is a monoclonal antibody that is directed against CD-20 positive cells. It is FDA-approved for the treatment of patients with chronic lymphocytic leukemia (CLL) who are refractory to both fludarabine and alemtuzumab-based therapies as well as the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate.

Efficacy:

Ofatumumab received FDA-approval for refractory CLL based on the results of an international, single-arm trial.²

- Patients with active CLL, ECOG PS 0-2 and refractory to at least one fludarabine-based regimen and either refractory or not a candidate for alemtuzumab-based therapy were eligible to participate.
- Results are from an interim analysis when 66 patients achieved the primary endpoint; the efficacy analysis is based on the fludarabine and alemtuzumab-refractory population (n=59).
- Of those refractory to fludarabine and alemtuzumab, the median age was 64 years (range, 41-86), 75% male; median number of prior therapies was 5; 93% received prior alkylating agents; 59% received prior rituximab; 88% received at least 8 infusions of ofatumumab; 54% received 12 infusions.
- ORR was 58% in FA-ref group, with a median PFS of 5.7 months and median OS of 13.7 months
- The authors note that the responses were independent of prior rituximab therapy; in the FA-ref group, ORR in those with prior rituximab was 19/35 (54%); ORR in those without prior rituximab was 15/24 (63%); median PFS with prior rituximab vs. no prior rituximab.

- Data from the phase 3 RESONATE trial comparing ibrutinib vs. ofatumumab in previously treated CLL or SLL (Small Lymphocytic Leukemia) reports that those receiving ibrutinib experienced longer PFS (primary endpoint) and an improvement in OS and ORR (secondary endpoints).

Approval in previously untreated CLL was based upon a randomized, open-label, parallel-arm study. Patients were randomized to receive either ofatumumab plus chlorambucil or chlorambucil alone.⁸

- A total of 447 previously untreated patients with CLL were randomized to ofatumumab plus chlorambucil or chlorambucil alone. Patients were considered inappropriate for fludarabine-based therapy (reasons included advanced age or concomitant comorbidities).
- Median age 69 years (range 35-92 yrs); 69% aged \geq 65 years; Male 63%; Caucasian 89%; 72% with \geq 2 concomitant comorbidities; 48% with CrCl \leq 70 ml/min
- Primary endpoint, PFS, was significantly improved with the combination vs. chlorambucil alone; 22.4 months vs. 13.1 months; HR 0.57 (0.45, 0.72); $p < 0.001$
- Secondary endpoints included Overall Response Rate (ORR) and Duration of Response (DOR). ORR 82.4% vs. 68.6% (ofatumumab + chlorambucil vs. chlorambucil alone); $p = 0.001$. Complete responses noted in 12 vs. 1%. Median DOR 22.1 vs. 13.2 months.

Safety:

Refractory CLL

- The most common adverse events (\geq 10%) noted in the refractory CLL clinical trial were infections, cough, diarrhea, anemia, fatigue, fever, neutropenia, dyspnea, nausea and rash.
- The most common serious adverse events noted were infections (pneumonia and sepsis), neutropenia and pyrexia. Infections were the most common adverse reaction leading to drug discontinuation in the clinical trials.
- Grade 3 or greater neutropenia was experienced by 42% of patients who had normal neutrophil counts at baseline. Grade 4 neutropenia was noted by 18% of patients; some had prolonged neutropenia lasting $>$ 2 weeks in duration.
- Serious adverse events may also include infusion-related reactions, bone marrow suppression, Progressive Multifocal Leukoencephalopathy (PML), Hepatitis B reactivation and intestinal obstruction.
- Infusion-related reactions occur with greatest frequency during the first infusion and lessen with subsequent infusions.

Previously Untreated CLL

- The most common adverse events (\geq 10%) noted in the previously untreated CLL trial included infusion reactions and neutropenia.
- The most common serious adverse events (grade 3 or greater) included infusion reactions and neutropenia.
- Prolonged neutropenia was reported in 6% of the ofatumumab/chlorambucil arm vs. 4% of the chlorambucil arm.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating ofatumumab for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Ofatumumab is an IgG 1 κ human monoclonal antibody. It binds to both extracellular loops of the CD20 molecule. The Fab domain of the antibody binds to the CD20 molecule while the Fc domain mediates immune functions to result in cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity and antibody-dependent, cell-mediated cytotoxicity.

Table #1	Pharmacokinetic Parameters
Parameter	Ofatumumab
Elimination	Dose-dependent clearance; due to B-cell depletion, clearance was reduced with subsequent infusions
Half-life	~ 14 days (range, 2.3 – 61.5 days)
V _{ss}	1.7 – 5.1 L

- Cross-study analyses were performed on patients with varied conditions (including 162 with CLL) who received ofatumumab in doses ranging from 100 – 2000 mg for the purpose of assessing the effect of body weight, age, gender and renal impairment on drug pharmacokinetics.
- Body weight: Clearance and volume of distribution increased as body weight increased. This increase was not deemed to be clinically significant. There is no dose adjustment recommended based on body weight.
- Age: Age (range, 21 – 86 years) did not significantly influence pharmacokinetics,
- Gender: Female patients were noted to have a 14-25% lower clearance and volume of distribution. These effects were not noted to be clinically important, therefore no dosage adjustment based on gender is recommended.
- Renal impairment: In patients with creatinine clearance values ranging from 33 – 287 ml/min, no clinically important effects were noted on ofatumumab pharmacokinetics.

FDA Approved Indication(s)

Ofatumumab is FDA-approved for the treatment of patients with chronic lymphocytic leukemia (CLL) that are refractory to fludarabine and alemtuzumab. The drug also received approval in combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate.

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Potential off-label uses of ofatumumab include treatment of Non-Hodgkins Lymphoma (NHL), in combination with cytotoxic chemotherapy for relapsed/refractory CLL, as monotherapy in first-line setting of CLL, Waldenstrom's Macroglobulinemia, treatment of rheumatoid arthritis multiple sclerosis, and B-cell malignancies with resistance to rituximab

Current Therapeutic Alternatives

Table 2. Select Therapeutic Options for Previously Untreated CLL

FDA approved for CLL	Drug and/or Regimen studied	Design	Population demo	ORR
Yes	Ofatumumab Approved for previously untreated patients with CLL in whom fludarabine-based therapy would be considered inappropriate and in patients with disease refractory to fludarabine and alemtuzumab			
	Ofatumumab (O) + chlorambucil (C) vs. chlorambucil (C) alone	Phase III	N=447; prev untreated	O + C vs. C PFS 22.4 vs. 13 months; P<0.001 ORR 82.4 vs. 69%; P=0.001 CR 12 vs. 1%
Yes	Fludarabine Approved for progressive disease during treatment with at least one standard alkylating-agent containing regimen			
	Fludarabine, cyclophosphamide, rituximab (FCR) vs. Fludarabine, rituximab (FR)	Phase II		FCR vs. FR ORR 95 vs. 90% CR 70 vs. 47%
	Fludarabine, cyclophosphamide (FC) vs. FC-Rituximab (FC-R)	Phase III [Hallek]	N=817; prev untreated	FC vs. FCR ORR 88 vs. 95% CR 22 vs. 44% PRS 33 vs 52 months OS 83 vs. 87%
	Fludarabine (F) vs. Chlorambucil (C)			F vs. C OS @ 6yrs: 43 vs. 38% OS @ 8yrs: 31 vs. 19%
Yes	Bendamustine Approval in untreated and relapsed CLL			
	Bendamustine + rituximab	Phase II	N=117; prev untreated	BR ORR 88% CR 23%
	Bendamustine (B) vs. Chlorambucil (C)		N=319; prev untreated	B vs. C ORR 68 vs. 31% PFS 22 vs. 8 months OS NS
Yes	Alemtuzumab – removed from US market in Sept. 2012 to plan for marketing under different name for treatment of MS; accessible through CLL distribution program			
	Alemtuzumab (A) Vs. Chlorambucil (C)	Phase III	N=297; prev untreated	A vs. C ORR 83 vs. 55% CR 24 vs. 2% PFS 15 vs. 12 months; p=0.0001
Yes	Pentostatin			
	Pentostatin + cyclophosphamide + rituximab (PCR) with GCSF	Phase II	N=64; prev untreated	PCR ORR 91% CR 41%
Yes	Chlorambucil			
	Chlorambucil (C) vs. Fludarabine (F)	Phase III	N=193; prev untreated; Median age 70; ECOG PS ≤ 2	C vs. F Median f/u 42 months: ORR 51 vs. 72% CR 0 vs. 7% PFS 18 vs. 19 months OS 64 vs. 46 mos (NS)
Yes	Obinutuzumab In combination with chlorambucil in previously untreated patients			
	Obinutuzumab + chlorambucil (OC) vs. Rituximab + chlorambucil (RC) vs. Chlorambucil (C)	Phase III Open-label Rand 1:2:2	N=781 Median age 73 yrs CrCl 62 ml/min CIRS baseline 8	C vs. OC vs. RC 3 mos after end of tx: ORR 31 vs. 77 vs. 65% CR 0 vs. 22 vs. 7% PR 31 vs. 55 vs. 58% PFS 11 vs. 27 vs. 16 mos

Table 3. Select Therapeutic Options for Relapsed/Refractory CLL

FDA approved for CLL	Drug and/or Regimen studied	Design	Population demo	ORR
Yes	Fludarabine Approved for progressive disease during treatment with at least one standard alkylating-agent containing regimen			
	Fludarabine monotherapy	Phase II	N=113; untreated vs. prior F	At 3 yrs: ORR 85 vs. 27%
	Fludarabine, cyclophosphamide (FC) vs. FC-Rituximab (FC-R)	Phase III	N=552; prior tx; Except no prior R	At 25 mos: PFS 20 vs. 30 mos
	Fludarabine, cyclophosphamide, mitoxantrone (FCM) vs. FCM-Rituximab (FCM-R)	Phase II	N=52; Rel/Ref; Median 2 prior tx; 63% prior F;	At 2 mos: ORR 58 vs. 65%; MRD negative: 3 vs. 5
Yes	Bendamustine Approval in untreated and relapsed CLL			
	Bendamustine + rituximab	Phase II	N=78; Rel/Ref	ORR 59%; CR 9% Gr ¼ tox 50%
	Bendamustine monotherapy	Phase I/II	N=16; Rel/Ref; Median 3 prior tx	PR 7; CR 2 Median DOR 43 mos
Yes	Alemtuzumab – removed from US market in Sept. 2012 to plan for marketing under different name for treatment of MS; accessible through CLL distribution program			
	Alemtuzumab monotherapy	Systematic review		ORR 38%; 6% CR
	Alemtuzumab monotherapy		No LAD vs. LAD < 5cm vs. LAD > 5cm	ORR 87 vs. 40 vs. 9%
	Alemtuzumab + fludarabine vs. Fludarabine alone	Phase III	N=335; Rel/Ref; 15% prior F	PFS 24 vs. 17 mos Gr ¼ tox 67 vs. 55%
	Alemtuzumab + rituximab		N=32; Rel/Ref	ORR 52%; CR 8% Infection rate 52%
	Fludarabine, cyclophosphamide, rituximab, alemtuzumab (CFAR)	Phase II	N=80; Rel/Ref	ORR 65%; CR 29% Infection rate 46%
Yes	Ibrutinib Approval after ≥ 1 prior therapy			
	Ibrutinib	Phase I/II	N=85; Rel/Ref; Median 4 prior tx	ORR 71%; CR 2%; At 26 mos, PFS 75%; OS 83%
	Ibrutinib (I) vs. ofatumumab (O)	Phase III	N = 391; Rel/Ref; I vs. O Prior tx: 3 vs. 2 ≥ 3 tx: 53 vs. 46% 11q22.3 del: 32 vs. 30% 17p13.1 del: 32 vs. 33%	I vs. O at 9.4 mos PFS: NR vs. 8.1 mos HR 0.22 (95% CI, 0.15-0.32; p<0.001) OS at 12 months OS: 90 vs. 81% HR 0.43 (95% CI, 0.24-0.79; p=0.005) ORR: 43 vs. 4% Odds ratio 17.4 (95% CI, 8.1-37.3; p<0.001)
Yes	Ofatumumab Approval in combination w/ chlorambucil in untreated CLL and treatment in patients refractory to F and A			
	Ofatumumab	Phase I/II	N=33; Rel/Ref; Median 3 prior tx	PR 44%/CR 0
	Ofatumumab	Phase II	N=138; Rel/Ref to F & A or F w/LAD > 5 cm; Median 5 prior tx	PR 58% prior fludarabine; PR 47% prior alemtuzumab; ORR independent of prior rituximab

Dosage and Administration¹

Note: Premedication slightly differs according to indication

Previously Untreated CLL premedications given 30 minutes to 2 hours prior to each dose:

- Acetaminophen 1000 mg orally (or equivalent)
- Cetirizine 10 mg or diphenhydramine 50 mg (or equivalent antihistamine, either IV or oral)
- Prednisolone 50 mg intravenously (or equivalent corticosteroid). If no Grade 3 or greater infusion-related event is noted during the first 2 ofatumumab infusions, the dose of corticosteroid may be reduced or omitted for subsequent infusions.

Refractory CLL premedications given 30 minutes to 2 hours prior to each dose:

- Acetaminophen 1000 mg orally (or equivalent)
- Cetirizine 10 mg or diphenhydramine 50 mg (or equivalent antihistamine, either IV or oral)
- Prednisolone 100 mg or equivalent intravenous corticosteroid*

* Corticosteroid dose reduction

- Do not reduce corticosteroid dose for ofatumumab infusions #1, 2 and 9.
- Corticosteroid doses may be reduced as follows:
 - Doses 3 through 8:
 - ✓ If infusion-related reaction \geq grade 3 experienced, do not reduce corticosteroid dose for subsequent doses.
 - ✓ If infusion-related reaction $<$ grade 3 experienced, may consider gradually reducing corticosteroid dose with subsequent doses.
 - Doses 10 through 12:
 - ✓ If infusion-related reaction \geq grade 3 experienced with dose #9, do not reduce corticosteroid dose for subsequent doses.
 - ✓ If infusion-related reaction $<$ grade 3 experienced with dose #9, may consider administering prednisolone 50 – 100 mg (or its equivalent) for subsequent doses.

Dosing/Administration

Note: Dose varies according to indication

- Ofatumumab should only be administered as an intravenous infusion.
- It should NOT be given as an intravenous bolus or push.
- Premedication before each infusion

Dose for Previously Untreated CLL

A total course of therapy consists of 12 doses administered as follows:

Ofatumumab 300mg initial dose, initiate infusion at a rate of 3.6 mg/hr (12 ml/hr) on Day 1, followed by 1000 mg on Day 8 (cycle 1) at rate of 25 mg/hr (25 ml/hr)*, then followed by 1000 mg on Day 1 of subsequent 28-day cycles for a minimum of 3 cycles until best response or a maximum of 12 cycles.

* Initiate infusion rate at 12 mg/hr if a Grade 3 or greater infusion-related adverse event was experienced during the previous infusion.

In the absence of an infusion-related adverse event, the rate of infusion may be increased every 30 minutes (see Table 4). Do not exceed the infusion rates in Table 4.

Table 4. Infusion rates for ofatumumab in previously untreated CLL

Interval after start of infusion (min)	Cycle 1, day 1 ^a (ml/hr)	Cycle 1, day 8 ^b and Cycles 2-12 ^c (ml/hr)
0-30	12	25
31-60	25	50
61-90	50	100
91-120	100	200
121-150	200	400
151-180	300	400
>180	400	400

^a Cycle 1, Day 1 = 300 mg; median duration of infusion = 5.2 hours

^b Cycle 1, Day 8 = 1000 mg; median duration of infusion = 4.4 hours

^c Cycles 2 through 12 = 1000 mg; median durations of infusion = 4.2 to 4.4 hours

Dose for Refractory CLL

A total course of therapy consists of 12 doses administered as follows*:

Dose 1: Ofatumumab 300mg initial dose, initiate infusion at a rate of 3.6 mg/hr (12 ml/hr), followed 1 week later by

Doses 2 through 8: 2000 mg weekly for 7 doses, then 4 weeks later,

Dose 2: Initiate infusion at rate 24 mg/hr (12 ml/hr)

Doses 3 – 12: initiate infusion at rate of 50 mg/hr (25 ml/hr)

Doses 9 through 12: 2000 mg every 4 weeks for 4 doses

* If no infusional toxicity, the rate of drug infusion may be increased every 30 minutes as described in Table 5. Do not exceed the listed infusion rates.

Table 5. Recommended Infusion Rates in the Absence of Infusional Toxicity in Refractory CLL

Interval After Start of Infusion (min)	Dose 1 (mL/hr)	Dose 2 (mL/hr)	Doses 3 – 12 (mL/hr)
0-30	12	12	25
31-60	25	25	50
61-90	50	50	100
91-120	100	100	200
> 120	200	200	400

Dose Modification

- Interrupt infusion for infusion-related reactions of any severity. Treatment can be resumed at the discretion of the treating physician. Use the following modifications as a guide.
- For Grade 1, 2 or 3 infusion-related reactions, If reaction resolves or remains \leq Grade 2, resume with following modifications:
 - Grade 1 or 2, infusion at 50% of previous rate
 - Grade 3 or 4, infuse at rate of 12 ml/hr
- After resuming the infusion, for Grade 1 – 3 reactions, the rate may be increased according to Tables 4 and 5, based on patient tolerance.
- Consider permanent discontinuation of ofatumumab if the severity of the infusion reaction does not resolve to less than or equal to Grade 2 despite adequate clinical intervention.
- Permanently discontinue therapy if patient experiences an anaphylactic reaction.

Preparation

- Ofatumumab is available as 100 mg/5ml (20mg/ml concentration) and 1000 mg/50ml single-use, preservative-free glass vials that should be stored under refrigeration and protected from light.
- Do not shake the product.
- Inspect drug products for particulate matter and discoloration prior to administration. The final product should be a colorless solution and may contain small amounts of visible translucent-to-white, amorphous, ofatumumab particles. Do not use if discolored, cloudy or if foreign particulate matter is visible.
- All doses should be prepared in 1000 ml of 0.9% Sodium Chloride Injection, USP

- To prepare a 300 mg dose:
 1. Withdraw/discard 15 ml of 0.9% Sodium Chloride Injection from 1000 ml polyolefin bag
 2. Withdraw 5 ml from each 100 mg vial of ofatumumab (3 x 100 mg)
 3. Add to 1000 ml bag
 4. Gently invert to mix
- To prepare a 1000 mg dose:
 1. Withdraw/discard 50 ml from 0.9% Sodium Chloride Injection, USP 1000 ml bag
 2. Withdraw 50 ml for a single-use 1000 mg vial of ofatumumab
 3. Add to 1000 ml bag
 4. Gently invert to mix
- To prepare a 2000 mg dose:
 1. Withdraw/discard 100 ml from 0.9% Sodium Chloride Injection, USP
 2. Withdraw 50 ml from each of 2 single-use 1000 mg vials of ofatumumab
 3. Add to 1000 ml bag
 4. Gently invert to mix
- Store diluted solution between 2° to 8°C (36° to 46°F)

Administration

- Do not mix the ofatumumab infusion with other medications.
- Use an infusion pump and an administration set.
- Flush the intravenous line with 0.9% Sodium Chloride Injection, USP before and after each dose.
- Begin infusion within 12 hours of preparation.
- Discard prepared solution after 24 hours.

Efficacy

Efficacy Measures for CLL

Chronic Lymphocytic Leukemia

The response criteria according to the National Cancer Institute-Sponsored Working Group Guidelines for CLL were used.^{5,7} Final assessment of best response was conducted by an Independent Committee for Response Assessment. Classification by this group was based on the NCI Group criteria.

Variable	NCI Working Group Criteria
Complete Response (CR)	
Physical exam	Normal
Symptoms	None
Lymphocytes (x 10 ⁹ /L)	≤ 4
Neutrophils (x 10 ⁹ /L)	≥ 1.5
Platelets (x 10 ⁹ /L)	> 100
Hgb (g/dL)	> 11 (untransfused & without erythropoietin)
Bone marrow lymphs (%)	Normocellular, < 30% lymphs; no nodules
Partial Response (PR)	
Physical exam (nodes, and/or liver, spleen)	≥ 50% decrease
Plus ≥ 1 of:	
Neutrophils (x 10 ⁹ /L)	≥ 1.5 or > 50% improvement over baseline
Platelets (x 10 ⁹ /L)	> 100 or ≥ 50% over baseline
Hgb (x 10 ⁹ /L)	> 11 or 50% improvement
Duration of CR or PR	≥ 2 months
Progressive Disease (PD)	

Physical exam (nodes, liver, spleen)	≥ 50% increase or new
Circulating lymphocytes	≥ 50% increase
Constitutional symptoms	Any
Circulating clonal b-lymphocytes	≥ 50% increase from baseline
Platelet count	≥ 50% decrease from baseline
Hemoglobin	> 2 g/dl decrease from baseline
Marrow	≥ 30% increase of lymphocytes from normal
Stable Disease (SD)	All others

Summary of efficacy findings

Previously Untreated CLL

In a randomized, open-label, parallel-arm fashion, previously untreated patients with CLL were randomized to receive ofatumumab plus chlorambucil (O + CHL) or chlorambucil (CHL) alone.

- A total of 447 previously untreated patients with CLL were randomized to ofatumumab plus chlorambucil or chlorambucil alone. Patients were included from 109 centers within 16 countries between Dec. 2008 and March 2013.
Ofatumumab dose: cycle #1: 300 mg on day 1 and 1000 mg on day 8
Subsequent cycles: 1000 mg on day 1 every 28 days
Chlorambucil dose: 10 mg/m² orally on days 1-7 every 28 days
Vs.
Chlorambucil alone: 10 mg/m² orally on days 1-7 every 28 days
Minimum of 3 cycles given and continued beyond maximal response for up to 12 cycles
- 60% of patients received 3-6 cycles of O + CHL; 30% received 7-12 cycles
- Patients were considered inappropriate for fludarabine-based therapy (reasons included advanced age or concomitant comorbidities)
- Key exclusions included:
Chronic or current active infection requiring treatment, positive serology for hepatitis B or HIV-positive
Clinically significant conditions including cardiac disease, cerebrovascular disease, past/current malignancy, compromised renal or liver function
High-dose steroids for any condition except for use of steroids in doses ≤ 100 mg/day hydrocortisone (or equivalent) for < 7 days (e.g. to treat asthma exacerbations)
- Median age 69 years (range 35-92 yrs); 69% aged ≥ 65 years; Male 63%; Caucasian 89%
- 72% with ≥ 2 concomitant comorbidities; 48% with CrCl ≤ 70 ml/min
- Primary endpoint, PFS, was significantly improved with O + CHL vs. CHL alone; 22.4 months vs. 13.1 months; HR 0.57 (0.45, 0.72); p< 0.001
- Secondary endpoints included Overall Response Rate (ORR) and Duration of Response (DOR). ORR 82.4% vs. 68.6% (O + CHL vs. CHL alone); p=0.001. Complete responses noted in 12 vs. 1%. Median DOR 22.1 vs. 13.2 months.

CLL Refractory to Fludarabine and Alemtuzumab

Ofatumumab received FDA-approval based on the results of an international, single-arm trial.²

- Patients with active CLL, ECOG PS 0-2 and refractory to at least one fludarabine-based regimen and either refractory or not a candidate for alemtuzumab-based therapy were eligible to participate.
- Treatment included eight weekly infusions of ofatumumab, followed by four monthly infusions.
- The initial ofatumumab dose was 300mg, subsequent doses were 2000mg.
- Assessments of disease status and response were performed every 4 weeks until week 28, then every 3 months until month 24. Responses must be maintained ≥ 2 months. Assessment was via Independent Review Committee, but imaging scans were not included for response assessment.
- The primary endpoint was ORR (including CR, nodular PR and PR) during the 24 week period. NCI-Working Group 1996 Guidelines for CLL were used.
- Results are from an interim analysis when 66 patients achieved the primary endpoint; the efficacy analysis is based on the fludarabine and alemtuzumab-refractory population (n=59).
- Of those refractory to fludarabine and alemtuzumab, the median age was 64 years (range, 41-86), 75% male; median number of prior therapies was 5; 93% received prior alkylating agents; 59% received prior rituximab; 88% received at least 8 infusions of ofatumumab; 54% received 12 infusions.
- ORR was 58% in FA-ref group, with a median PFS of 5.7 months and median OS of 13.7 months
- The authors note that the responses were independent of prior rituximab therapy; in the FA-ref group, ORR in those with prior rituximab was 19/35 (54%); ORR in those without prior rituximab was 15/24 (63%); median PFS with prior rituximab vs. no prior rituximab was 5.5 vs. 7.1 months.

RESONATE (Study of Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia) trial was stopped at the point of preplanned interim analysis.

- A total of 391 patients at 67 sites were enrolled throughout the U.S., Australia and Europe. Enrolled patients had a diagnosis of CLL or SLL, had received at least one prior therapy and were considered to be inappropriate for purine analog therapy (due to short PFS after chemoimmunotherapy or because of concomitant illness, age ≥ 70 years, or possessed a chromosome 17p13.1 deletion. Patients were required to have ECOG PS < 2 , adequate bone marrow, hepatic and liver function. Those requiring warfarin or strong CYP3A4/5 inhibitors were excluded.
- Participants were randomized to ibrutinib 420 mg PO daily or ofatumumab for up to 24 weeks (initial dose 300 mg at week 1, then 2000 mg weekly x 7 weeks, then every 4 weeks x 16 weeks. Stratification was done according to purine analog chemoimmunotherapy resistance and presence/absence of chromosome 17p13.1 deletion. The primary endpoint was PFS (assessed by IRC) with secondary endpoints of OS and ORR.
- At the median follow-up of 9.4 months, the median duration of PFS was not reached versus median duration of PFS of 8.1 months with ofatumumab. The hazard ratio for progression or death was 0.22 (95% CI, 0.15-0.32; $p < 0.001$) for ibrutinib – a 78% reduction in the risk of progression/death compared to those receiving ofatumumab. The subgroup analysis noted that the effect on PFS was observed regardless of baseline or molecular characteristics.
- Patients with chromosome 17p13.1 deletion also appreciated the improvement in PFS. A total of 127 patients with chromosome 17p13.1 deletion were included in RESONATE (63 received ibrutinib; 64 received ofatumumab). The median PFS had not been reached for the ibrutinib subset of patients, while it was estimated to be 5.8 months in the ofatumumab arm [HR 0.25 (95% CI 0.14-0.45)]. The ORR was 47.6 vs. 4.7% in the

- ibrutinib vs. ofatumumab arms, respectively. All responses were partial; no patients achieved a complete response.
- At 6 months, 83% vs. 49% of ibrutinib vs. ofatumumab patients were alive with no progressive disease. The secondary endpoint of OS was prolonged in the ibrutinib arm (HR 0.43; 95% CI 0.24-0.79; P=0.005), reducing the risk of death by 57%. Although 57 patients originally randomized to ofatumumab crossed over to receive ibrutinib, the survival effect was based on analyses censored at the time of crossover. The overall response rate was higher for the ibrutinib vs. ofatumumab arm, respectively (42.5 vs. 4.1%; p< 0.001). Neither arm reported any complete responses, only partial ones.

Adverse Events (Safety Data)^{1,2}

Previously Untreated CLL: Safety data was evaluated in an open-label, parallel-arm, randomized study of 444 patients. The median number of ofatumumab cycles completed was six.

Refractory CLL: Safety data was evaluated in 181 patients with relapsed or refractory CLL within two open-label, non-randomized, single-arm studies. Approximately 90% of patients received at least 8 infusions while 55% received all 12 infusions.

Deaths and Other Serious Adverse Events

Serious adverse events may include infusion-related reactions, bone marrow suppression, Progressive Multifocal Leukoencephalopathy (PML), Hepatitis B Reactivation and intestinal obstruction.

The most common serious adverse events noted were infections (pneumonia and sepsis), neutropenia and pyrexia. Infections were the most common adverse reaction leading to drug discontinuation in the clinical trials. A total of 108 patients (70%) experienced bacterial, viral or fungal infections. Infections considered \geq grade 3 were noted in 29% of patients, of which 12% were fatal. In the FA-ref group, 17% had fatal infections.

Grade 3 or greater neutropenia was experienced by 42% of patients who had normal neutrophil counts at baseline. Grade 4 neutropenia was noted by 18% of patients; some had prolonged neutropenia lasting > 2 weeks in duration.

The FDA-review notes that myocardial infarction / angina was noted in four patients within two days of receiving a dose of ofatumumab. Due to characteristics of the patient population and single-arm design of the trial, a direct relationship cannot be made to ofatumumab therapy.

Common Adverse Events

Refractory CLL: The most common adverse events (\geq 10%) noted in the clinical trial were infections, cough, diarrhea, anemia, fatigue, fever, neutropenia, dyspnea, nausea and rash.

RESONATE data reports reduced creatinine clearance (any grade) in 16 vs. 17% of ibrutinib vs. ofatumumab patients, respectively

Previously Untreated CLL: The most common adverse events (\geq 10%) were infusion reactions and neutropenia.

Infusion-related reactions occur with greatest frequency during the first infusion and lessen with subsequent infusions. Wierda et al. note that 38% of patients experienced an infusion-related

reaction during their first infusion while only to 7% of patients experienced a reaction at their 12th infusion.²

Other Adverse Events

Table #6 Incidence of AEs occurring in > 5% of study patients in refractory CLL setting

AE	Total population (n=154)		FA-ref population (n=59)	
	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)
Infections				
Pneumonia	23	14	25	15
URI	11	0	3	0
Bronchitis	11	< 1	19	2
Sepsis	8	8	10	10
Nasopharyngitis	8	0	8	0
Herpes Zoster	6	1	7	2
Sinusitis	5	2	3	2
Anemia	16	5	17	8
Insomnia	7	0	10	0
Headache	6	0	7	0
Cardiovascular				
HTN	5	0	8	0
Hypotension	5	0	3	0
Tachycardia	5	< 1	7	2
Respiratory				
Cough	19	0	19	0
Dyspnea	14	2	9	5
Gastrointestinal				
Diarrhea	18	0	19	0
Nausea	11	0	12	0
Skin disorders				
Rash	14	<1	17	2
Urticaria	8	0	5	0
Hyperhidrosis	5	0	5	0
Musculoskeletal				
Back pain	8	1	12	2
Muscle spasms	5	0	3	0
General				
Pyrexia	20	3	25	5
Fatigue	15	0	15	0
Peripheral edema	9	<1	8	2
Chills	8	0	10	0

Table #7 Incidence of AEs occurring in ≥ 5% of study patients receiving ofatumumab + chlorambucil and also ≥ 2% more than patients receiving chlorambucil

AE	Ofatumumab + Chlorambucil (n=217)		Chlorambucil (n=227)	
	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)
Infusion reactions	67	10	0	0
Neutropenia	27	26	18	14
Asthenia	8	<1	5	0
Headache	7	<1	3	0
Leukopenia	6	3	2	<1
Herpes simplex	6	0	4	<1
Lower RTI	5	1	3	<1
Arthralgia	5	<1	3	0
Upper abdominal pain	5	0	3	0

Table #8 post-baseline hematologic lab abnormalities occurring with ≥ 5% incidence in patients receiving ofatumumab + chlorambucil and also ≥ 2% more than patients receiving chlorambucil

AE	Ofatumumab + Chlorambucil (n=217)		Chlorambucil (n=227)	
	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)
Leukopenia	67	23	28	4
Neutropenia	66	29	56	24
Lymphopenia	52	29	20	7
Arthralgia	5	<1	3	0
Upper abdominal pain	5	0	3	0

Infusion Reactions in previously untreated patients

A total of 67% of patients receiving ofatumumab + chlorambucil experienced symptoms of infusion reactions (10% were grade 3 or 4). The majority occurred with earlier cycles and decreased with subsequent infusions: cycle #1, day #1 (56% overall; 6% grade 3 or 4); day #8 (23% overall; 3% grade 3 or 4).

Infusion reactions in relapsed/refractory CLL patients

A total of 44% of patients experienced infusion reactions on day #1 while 29% experienced reactions on day #2.

Infections

A total of 70% of patients experienced bacterial, viral or fungal infections with 29% experiencing grade 3 or greater infections (12% fatal; 17% fatal in the fludarabine- and alemtuzumab-refractory group).

Tolerability

Ofatumumab may have limited tolerability in some patients. In the refractory CLL population, Wierda et al. reports that 90% of patients received at least 8 infusions while only 54% of the study population received all 12 infusions. A course of therapy consists of 12 doses.

In the previously untreated CLL population, the median number of ofatumumab cycles completed was six.

Postmarketing experience includes the following:

Infusion-related cardiac events: cardiac arrest

Mucocutaneous reactions: Stevens-Johnson syndrome, porphyria cutanea tarda

Contraindications

None listed in the package insert.

Warnings and Precautions**Boxed Warning: Hepatitis B Virus Reactivation and Progressive Multifocal Leukoencephalopathy**

- **Hepatitis B Virus (HBV) reactivation can occur in patients receiving CD20-directed cytolytic antibodies, including ofatumumab, in some cases resulting in fulminant hepatitis, hepatic failure and death.**
- **Progressive Multifocal Leukoencephalopathy (PML) resulting in death can occur in patients receiving CD20-directed cytolytic antibodies, including ofatumumab.**

Infusion Reactions

Serious infusion-related reactions manifest as bronchospasm, dyspnea, laryngeal and pulmonary edema, flushing, hypertension, hypotension, syncope, cardiac ischemia/infarction, back pain, abdominal pain, pyrexia, rash, urticaria and angioedema. Infusion-related reactions occur with a higher frequency with the first 2 infusions.

It is recommended to premedicate with acetaminophen, an antihistamine and a corticosteroid. Ofatumumab infusions should be interrupted for infusion reactions of any severity. Immediate medical management should begin for severe infusion reactions such as angina or indicators of potential myocardial ischemia.

Cytopenias

Severe neutropenia and thrombocytopenia, lasting \geq 1 week can occur with ofatumumab therapy.

Grade 3 or 4 late-onset neutropenia (at least 42 days after last treatment dose) and/or prolonged neutropenia (unresolved between 24-42 days after last treatment dose) has been reported in patients receiving ofatumumab.

Complete Blood Counts (CBC) and platelet counts should be monitored at regular intervals during and after the conclusion of therapy. Patients who develop Grade 3 or 4 cytopenias should be monitored with greater frequency.

Progressive Multifocal Leukoencephalopathy (PML)

PML can occur with ofatumumab therapy. Fatal cases have been reported. In any patient exhibiting neurologic changes, whether new onset or changes in pre-existing neurologic condition, consider PML. Discontinue ofatumumab if PML is suspected. Initiate further evaluation including consultation with a neurology specialist.

Hepatitis B Reactivation

Hepatitis B virus (HBV) reactivation has occurred in patients receiving ofatumumab. Some of these cases resulted in fulminant hepatitis, hepatic failure and death. Reactivation has been reported in patients who are hepatitis B surface antigen (HBsAg) positive and those who are HBsAg negative, but hepatitis B core antibody (anti-HBc) positive. Reactivation has also been reported in patients who appeared to have resolved hepatitis B infection (i.e. HBsAg negative, anti-HBc positive and anti-HBs positive).

Screen all patients for HBV infection (measure HBsAg and anti-HBc) before beginning therapy with ofatumumab. For patients with evidence of hepatitis B infection, consult a specialist for monitoring recommendations and consideration of HBV antiviral therapy.

Patients with current or prior HBV infection should be monitored throughout therapy and for several months following the conclusion of therapy. HBV reactivation has been reported for at least 12 months following completion of therapy.

Immediately discontinue ofatumumab and concomitant chemotherapy in patients who develop HBV reactivation and begin appropriate treatment. Discuss the possibility of restarting ofatumumab therapy with a specialist with expertise in managing hepatitis B. There is insufficient data regarding the safety of resuming ofatumumab in patients who develop HBV reactivation.

Hepatitis B Virus Infection

Fatal infection due to hepatitis B virus in patients with no prior infection has been reported with ofatumumab. Monitor patients for clinical and laboratory signs of hepatitis.

Immunizations

Do not administer live viral vaccines to patients who currently or recently received ofatumumab therapy. The safety of live vaccines is unknown. It is unclear if the ability to mount an immune response to a vaccine is impaired while receiving ofatumumab therapy, as this has not been studied.

Tumor Lysis Syndrome (TLS)

TLS has been reported in patients who have received ofatumumab. Those at highest risk are those with a high tumor burden and/or high circulating lymphocyte counts ($>25 \times 10^9 /L$). TLS prophylaxis with anti-hyperuricemics and hydration should begin 12-24 hours prior to ofatumumab therapy.

Use in Specific Populations

Pregnancy

Pregnancy Category C. Pregnant women were excluded from clinical trials with ofatumumab. There are no data on the use of ofatumumab in human pregnancy. Use during pregnancy should be considered only if the potential benefit to the mother justifies the potential risk to the fetus.

In a reproductive animal study, ofatumumab crossed the placental barrier and resulted in depletion of peripheral B-cells and reduced spleen and placental weights. The effects of perinatal B-cell depletion in the fetus and the kinetics of B-cell recovery are unknown at this time.

Nursing Mothers

It is unknown if ofatumumab is excreted in breast milk. Human IgG is secreted in human milk although it is not believed that infants absorb substantial amounts. Due to the unknown effects, caution should be taken whenever ofatumumab is given to a nursing woman.

Geriatric Use

In refractory CLL, there have not been sufficient numbers of patients over the age of 65 to determine if response is different than in younger individuals.

In the previously untreated CLL population, 68% of patients receiving ofatumumab plus chlorambucil were aged 65 years and older. These patients experienced a higher incidence of the following grade 3 or 4 adverse events compared to their younger counterparts: neutropenia (30 vs. 17%), pneumonia (5 vs. 1%). Also, 29% of older patients experienced serious adverse events compared with 13% who were younger than 65 years. No clinically meaningful differences in the effectiveness of ofatumumab plus chlorambucil were noted between older and younger patients.

Renal Impairment

No formal studies have been conducted in this patient population.

Hepatic impairment

No formal studies have been conducted in this patient population.

Sentinel Events

Hepatitis B reactivation, resulting in hepatitis, liver failure and death, has been reported in patients receiving ofatumumab. In addition, Progressive multifocal leukoencephalopathy (PML) has resulted in death.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

LA/SA for generic name ofatumumab: efalizumab, obinutuzumab, omalizumab

LA/SA for trade name Arzerra™: Asclera™

Drug Interactions

Drug-Drug Interactions

- Would caution that other myelosuppressive therapies given concomitantly may compound myelosuppressive effects of ofatumumab.

- The safety of live viral vaccines during or following treatment with ofatumumab has not been studied. Do not administer live viral vaccines to patients who have recently received ofatumumab. It is unclear if the ability to mount an immune response to a vaccine is impaired while receiving ofatumumab therapy, as this has not been studied.
- Coadministration of ofatumumab with chlorambucil did not result in clinically pertinent effects on the pharmacokinetics of chlorambucil or its active metabolite, phenylacetic acid mustard.

Acquisition Costs

Refer to VA pricing sources for updated information.

Pharmacoeconomic Analysis

There have not been any published pharmacoeconomic evaluations of this drug to date.

Conclusions

Outcome in clinically significant area	CLL Relapsed/Refractory (R/R): ORR CLL (previously untreated): PFS
Effect Size	CLL (R/R): ORR 58%, PFS 5.7 months, OS 13.7 months CLL (previously untreated): PFS 22 vs 13 months; HR 0.57 (0.45, 0.72); p< 0.001
Potential Harms	Neutropenia (all grades) 66%; (gr 3, 4) 42% Infections (all grades) 70%; (gr 3,4) 29% Infusion-related reactions w/first infusion: 38%
Net Clinical Benefit	CLL (R/R): Moderate CLL (previously untreated): Moderate

Definitions

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life

Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio

Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)

Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Refractory CLL

Ofatumumab gained accelerated FDA-approval on the premise that therapy is reasonably likely to provide clinical benefit in a patient population with limited treatment options and life-threatening illness. The population described is considered to be refractory to fludarabine and alemtuzumab (also known as double refractory or DR) and in which the majority (> 90%) failed alkylator-based therapy.

Treatment options for fludarabine and alemtuzumab-refractory CLL are limited. There is no standard therapy for these patients at this stage in their disease. Tam et al. reports on the natural history and outcome of salvage therapy in this population of 93 patients⁶. They report an overall response rate range of 13 - 38% and a median overall survival of 9 months for various single-agent cytotoxics, monoclonal antibodies and combination chemotherapy regimens. Of note, SCT was not included in their evaluation.

The approval of ofatumumab was based on the prior FDA precedent, which was approval of alemtuzumab in 2001³. Alemtuzumab provided an ORR of 21 – 33% with a median duration of response ranging from 7 – 11 months. Ofatumumab provided an ORR of 42% (99% CI: 26, 60) and a median duration of response of 6.5 months. There were no complete responses.

Infections were common in a significant portion of the study population. Due to the high rate of infections in this population at baseline and single-arm design of the trial, it is difficult to ascertain the additional infection risk imposed by ofatumumab. The high incidence of drug-induced neutropenia may increase the risk of infection. In addition, B-lymphocytes are depleted for a prolonged duration. The relationship between ofatumumab and cardiovascular events (ie. infarction, angina) needs to be further evaluated in clinical trials. Although data reports that ofatumumab is a well-tolerated therapy, the adverse effect profile is significant, especially in a heavily pre-treated CLL population.

Since approval of ofatumumab, other therapies for relapsed/refractory CLL have entered the market. Data from the RESONATE trial, a phase 3 study, indicates that ibrutinib, a Bruton's tyrosine kinase inhibitor, results in a significant improvement in outcomes when compared to ofatumumab therapy. Progression-Free Survival, Overall Survival and Objective Response Rates were significantly greater with ibrutinib. These data, which show an inferior response to ibrutinib in the relapsed/refractory CLL setting, in combination with factors such as a milder toxicity profile and formulation (ibrutinib is oral while ofatumumab is injectable), will limit the use of ofatumumab.

Previously Untreated CLL (for whom fludarabine is considered inappropriate)

In an open-label, phase 3 study design, patients that were previously untreated for CLL were randomized to receive either ofatumumab in combination with chlorambucil or chlorambucil alone. The patients included in the study were not candidates for fludarabine either due to advanced age or concomitant comorbidities. PFS, the primary endpoint, was significantly longer with the combination vs. monotherapy by approximately 9 months. In addition, ORR and CR rates were higher, as well as the median duration of response.

The dosing of ofatumumab for the previously untreated CLL indication is different from the relapsed/refractory dose. Infusion-related reactions were still noted in a significant number of patients, and require premedication with close monitoring. Cytopenias, particularly neutropenia, with late-onset and prolonged duration were common within the clinical trial setting. The infection risk is high with ofatumumab and includes infections of bacterial, viral and fungal origin. Risk potential for tumor lysis syndrome should be assessed prior to administration of ofatumumab and chlorambucil therapy with initiation of anti-hyperuricemic therapy, hydration and close monitoring.

Although studied in an older population with comorbidities, use of ofatumumab and chlorambucil will require that providers pay particular attention to individual patient factors when considering this regimen, as the toxicities of this combination may be difficult to tolerate.

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Prepared September 2010, Updated August 2014

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