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Ofatumumab: A New Agent for Chronic Lymphocytic Leukemia

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H&O How is ofatumumab different from other anti-CD20 antibodies such as rituximab? How is it effective?

AO Ofatumumab (Arzerra, GlaxoSmithKline/Genmab) is a fully human, high-affinity monoclonal antibody whose epitope on the CD20 molecule of B cells is distinct from that of rituximab (Rituxan, Genentech). It binds to other residues on the CD20 molecule, including the membrane-proximal small loop which may elicit potent in vitro complement-dependent cytotoxicity (Figure 1). Ofatumumab also has a slower off rate from the receptor, and preclinical work has indicated that the agent may be superior to rituximab at corresponding dose levels in killing B-cell lines with low CD20 expression.

In 2008, Dr. Bertrand Coiffier and colleagues published results from a safety and efficacy analysis of ofatumumab. In this dose-escalating study that included 33 patients with relapsed chronic lymphocytic leukemia (CLL), 3 cohorts of patients were given 4 weekly infusions of ofatumumab at 1 dose of 100 mg and 3 doses of 500 mg; 1 dose of 300 mg and 3 doses of 1,000 mg; or 1 dose of 500 mg and 3 doses of 2,000 mg. The median number of previous treatments in these patients was 3; 67% of the patients were Binet stage B. The majority of related adverse events occurred at first infusion and decreased at each subsequent infusion. The response rate in patients who received 1 dose of 500 mg and 3 doses of 2,000 mg was 50%, with 1 patient having a nodular partial remission and 12 patients having partial remission. In conclusion, ofatumumab was found to be well tolerated in patients with CLL in doses up to 2,000 mg.[1]

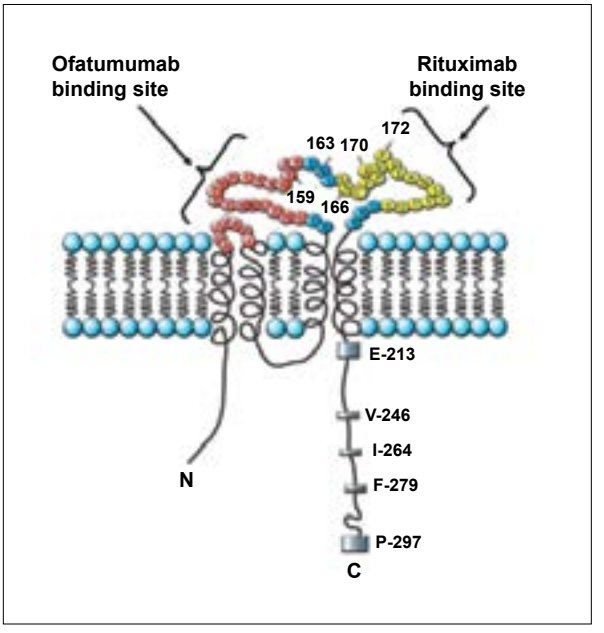

Figure 1. Ofatumumab characteristics

Figure image provided by Joost M. Bakker, PhD (Genmab). Data from Timmerman P, et al. *Open Vaccine J*. 2009;2:56-67 and Teeling JL, et al. *J Immunol*. 2006;177:362-371.

Table 1. Ongoing Trials Assessing Safety and Efficacy of Ofatumumab

Clinical Trial	NCT Number (clinicaltrials.gov)	Disease State	Active (Y/N)	Enrolling (Y/N)
Phase III ofatumumab + chlorambucil versus chlorambucil in first-line CLL	NCT00748189	CLL	Y	Y
Phase III O-FC versus FC in relapsed CLL	NCT00824265	CLL	Y	Y
Phase III ofatumumab versus rituximab in combination with chemotherapy (+DHAP or DVD) followed by ASCT in relapsed/refractory DLBCL	NCT01014208	DLBCL	Y	N
Phase II O-FC in first-line CLL	NCT00410163	CLL	Y	N
Phase II ofatumumab in fludarabine- and alemtuzumab-refractory CLL	NCT00349349	CLL	Y	N
Phase II ofatumumab retreatment and maintenance in refractory CLL	NCT00802737	CLL	Y	Y
Phase II ofatumumab in relapsed DLBCL not eligible/ relapsed after transplant	NCT00622388	DLBCL	Y	N
Phase II O+ICE/DHAP in relapsed refractory DLBCL prior to ASCT	NCT00823719	DLBCL	Y	Y
Phase II O-CHOP in first-line follicular NHL	NCT00494780	FL	Y	N
Phase II ofatumumab in rituximab-refractory follicular NHL	NCT00394836	FL	Y	N
Phase II ofatumumab in Waldenstrom's macroglobulinemia	NCT00811733	WM	Y	Y
Phase I ofatumumab in Japanese patients with CD20+ follicular NHL or CLL	NCT00742144	FL/CLL	Y	N

ASCT=autologous stem cell transplant; CLL=chronic lymphocytic leukemia; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; DHAP=cisplatin, cytarabine, dexamethasone; DLBCL=diffuse large B-cell lymphoma; DVD=dexamethasone, doxorubicin, vincristine; FC=fludarabine, cyclophosphamide; FL=follicular non-Hodgkin lymphoma; ICE=carboplatin, etoposide, ifosfamide; NHL=non-Hodgkin lymphoma; O=ofatumumab; WM= Waldenstrom's macroglobulinemia.

Also in 2008, we presented interim results from a multicenter phase II study of ofatumumab in CLL patients (n=138) refractory to both fludarabine and alemtuzumab (Campath, Genzyme) or fludarabine-refractory patients with bulky lymphadenopathy unsuitable for alemtuzumab. Patients, who were premedicated with paracetamol, antihistamine, and glucocorticoid, received 8 weekly infusions of ofatumumab followed by 4 monthly infusions (dose 1: 300 mg; doses 2–12: 2,000 mg). The overall response rate (ORR), assessed by an Independent Review Committee, was 58% in patients refractory to both fludarabine and alemtuzumab and 47% in patients with bulky lymphadenopathy who were refractory to fludarabine. Response was significantly correlated with longer survival (landmark analysis) for both groups. Overall, ofatumumab was shown to be effective across all major subgroups and well tolerated with no unexpected toxicities. We concluded that ofatumumab is a promising active treatment option with clinical benefit for patients with very poor prognosis who have exhausted standard treatment options.[2]

On October 26, 2009, the U.S. Food and Drug Administration approved ofatumumab for treating CLL patients who are refractory to both fludarabine and alemtuzumab. The antibody is also being studied as a possible treatment for other diseases such as various subtypes of non-Hodgkin lymphoma (NHL), rheumatoid arthritis, relapsing-remitting multiple sclerosis.

H&O What are the toxicity profiles for ofatumumab?

AO In the pivotal trial, the most common adverse reactions reported during ofatumumab therapy were neutropenia, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infections; the most common serious adverse reactions seen are infections including pneumonia and sepsis, neutropenia, and pyrexia.

Approximately 40% of patients developed primarily grade 1–2 flu-like reactions during the first infusion, but these symptoms gradually declined. Compared with historical controls, ofatumumab did not seem to increase the risk of severe infection. The median hemoglobin concentration and platelet counts increased during treatment, whereas the median neutrophil count was relatively stable during the 24 weeks of therapy.

H&O What were the updates presented at the 2009 American Society of Hematology (ASH) meeting?

AO At the 2009 ASH meeting, we presented data on the relationships between baseline factors and ofatumumab pharmacokinetics, and pharmacokinetic parameters and treatment outcomes taken from the aforementioned phase II pivotal trial.[3] Higher C_{max} at dose 1 was, as expected, associated with a lower tumor burden. Importantly, higher C_{max} and area under the curve at dose 8 (last weekly dose) were associated with increased likelihood of response and a longer progression-free survival (PFS).

At the ASH meeting in 2009, Dr. William Wierda and colleagues presented results from an international, randomized, phase II trial with 2 doses of ofatumumab combined with fludarabine and cyclophosphamide in previously untreated patients with CLL; 61 previously untreated patients with active CLL were randomized to receive either 500 mg or 1,000 mg of ofatumumab on day 1, combined with daily fludarabine (25 mg/m^2) and cyclophosphamide (250 mg/m^2) on days 1–3, every 4 weeks for a total of 6 courses. In both groups, the first dose of ofatumumab was 300 mg. The complete response rate was 32% for those who received 500 mg of ofatumumab compared with 50% for those who received 1,000 mg of ofatumumab; the ORR was 77% and 73%, respectively. The median PFS was not reached at the median follow-up of 8 months. No grade 3–4 infusion-related reactions on the day of ofatumumab infusion were reported. Investigators concluded that this combination regimen is highly active in previously untreated CLL patients.[4]

H&O What advancements with ofatumumab can we expect in the next few years?

AO Many trials are scheduled to assess the efficacy and safety of this agent in various diseases (Table 1). Some important tasks are to establish the effectiveness in combination with chemotherapy and to find ways to improve prognosis by effective immune-based therapies in elderly patients, who may not be able to tolerate intensive chemoimmunotherapy combinations. Another important goal is to conduct randomized trials on maintenance therapy in CLL patients; part of this approach relates to identifying the optimal dose for maintenance (when the tumor burden is small).

References

1. Coiffier B, Lepretre S, Pedersen LM, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. *Blood.* 2008;111: 1094-1100.

2. Österborg A, Kipps TJ, Mayer J, et al. Ofatumumab (HuMax-CD20), a novel CD20 monoclonal antibody, is an active treatment for patients with CLL refractory to both fludarabine and alemtuzumab or bulky fludarabine-refractory disease: results from the planned interim analysis of an international pivotal trial. *Blood (ASH Annual Meeting Abstracts)*. 2008;112:328.

3. Österborg A, Ronn BB, Jewell RC, et al. Correlation between serum ofatumumab concentrations, baseline patient characteristics and clinical outcomes in patients with fludarabine-refractory chronic lymphocytic leukemia (CLL) treated with single-agent ofatumumab. *Blood (ASH Annual Meeting Abstracts).* 2009;114: Abstract 3433.

4. Wierda WG, Kipps TJ, Dürig J, et al. Ofatumumab combined with fludarabine and cyclophosphamide (O-FC) shows high activity in patients with previously untreated chronic lymphocytic leukemia (CLL): results from a randomized, multicenter, international, two-dose, parallel group, phase II trial. *Blood (ASH Annual Meeting Abstracts).* 2009;114: Abstract 207.