Epratuzumab, a Humanized Anti-CD22 Antibody, in Aggressive Non-Hodgkin’s Lymphoma: Phase I/II Clinical Trial Results

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ABSTRACT

Purpose: We conducted a single-center, dose-escalation study evaluating the safety, pharmacokinetics, and efficacy of epratuzumab, an anti-CD22 humanized monoclonal antibody, in patients with aggressive non-Hodgkin’s lymphoma.

Experimental Design: Epratuzumab was administered once weekly for 4 weeks at 120-1000-mg/m² doses to 56 patients [most (n = 35) with diffuse large B-cell lymphoma].

Results: Patients were heavily pretreated (median, 4 prior therapies), 25% received prior high-dose chemotherapy with stem cell transplant, and 84% had bulky disease (≥5 cm). Epratuzumab was well tolerated, with no dose-limiting toxicity. Most (95%) infusions were completed within 1 h. The mean serum half-life was 23.9 days. Across all dose levels and histologies, objective responses (ORs) were observed in five patients (10%; 95% confidence interval, 3–21%), including three complete responses. In patients with diffuse large B-cell lymphoma, 15% had ORs. Overall, 11 (20%) patients experienced some tumor mass reduction. Median duration of OR was 26.3 weeks, and median time to progression for responders was 35 weeks. Two responses are ongoing at ≥34 months, including one rituximab-refractory patient.

Conclusions: These data demonstrate that epratuzumab has a good safety profile and exerts antitumor activity in aggressive non-Hodgkin’s lymphoma at doses of ≥240 mg/m², thus warranting further evaluation in this clinical setting.

INTRODUCTION

Non-Hodgkin’s lymphomas (NHLs), a heterogeneous group of cancers principally arising from B lymphocytes, represent approximately 4% of all newly diagnosed cancers (1). Aggressive NHL comprises approximately 30–40% of adult NHL (2) and includes diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), peripheral T-cell lymphoma, and anaplastic large cell lymphoma. Frontline combination chemotherapy cures less than half of the patients with aggressive NHL, and most patients eventually succumb to their disease (3).

For nearly three decades, the combination chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been the standard initial therapy for aggressive NHL. Clinical trials comparing CHOP with more toxic second- and third-generation chemotherapy regimens showed no advantage of the newer regimens over CHOP (4, 5). For patients with relapsed chemotherapy-sensitive aggressive NHL, the standard of care in most settings is high-dose chemotherapy and autologous stem cell transplantation [ASCT (6)]. However, most patients who die of aggressive NHL either are not candidates for ASCT (3) or relapse after ASCT. After decades of very little progress in the outcomes for patients with aggressive NHL, a number of promising therapies have recently emerged. These include the use of colony-stimulating factors to allow dose escalation of active but myelosuppressive agents (as in the CHOP-14 regimen) and monoclonal antibodies (7, 8).

Rituximab [Rituxan; Genentech, Inc. (South San Francisco, CA) and IDEC Pharmaceutical Corp. (San Diego, CA)], a chimeric (mouse/human) anti-CD20 monoclonal antibody, was the first therapeutic antibody approved by the United States Food and Drug Administration for treatment of relapsed or refractory low-grade or follicular NHL. Approval was based on a total of 166 patients with indolent NHL who had an overall response rate of 48% and a complete remission rate of 6% (9). Rituximab single-agent activity as second-line treatment in pa-
Epratuzumab in Aggressive NHL

patients with aggressive NHL (DLBCL or MCL) has been somewhat lower. In a Phase II study, Coiffier et al. (10) reported a response rate of 37% in patients with DLBCL (n = 30) and 33% in patients with MCL (n = 12). A retrospective review of a clinical pharmacology database identified 17 patients who were refractory to or relapsed after ASCT and had a higher objective response (OR) rate to rituximab as a single agent (54% in DLBCL and 50% in MCL; Ref. 11). Clinical trials have shown that rituximab in combination with CHOP as first-line therapy in older patients with DLBCL provides a statistically significant survival benefit over CHOP (12). Consequently, this combination therapy has recently been approved in Europe as a first-line therapy in DLBCL patients ages 60 years or older, whereas a United States intergroup study of CHOP with rituximab is currently undergoing evaluation. Rituximab continues to be evaluated in a variety of other settings and indications, both as a single agent and in combination with other therapies.

Other B-cell antigens, such as CD19, CD22, and CD52, represent targets of therapeutic potential for treatment of lymphoma (13). CD22 is a 135-kDa B-cell-restricted sialoglycoprotein expressed on the B-cell surface only at the mature stages of differentiation (14). In B-cell NHL, CD22 expression ranges from 91% to 99% in the aggressive and indolent populations, respectively (15). Using immunohistochemistry staining of formalin-fixed paraffin-embedded samples, CD22 positivity has shown to be highly variable between samples and within the same samples in terms of the percentage of positive cells, intensity of staining, and localization (i.e., membrane versus cytoplasm). The function of CD22 is uncertain, although studies have implicated roles for the antigen both as a component of the B-cell activation complex (16) and as an adhesion molecule (17). The B cells of CD22-deficient mice have a shorter life span and enhanced apoptosis, which suggests a key role of this antigen in B-cell survival (18). After binding with its natural ligand(s) or antibodies, CD22 is rapidly internalized, providing a potent costimulatory signal in primary B cells and proapoptotic signals in neoplastic B cells (19).

The LL2 antibody (formerly called HPB-2) is an IgG2a mouse monoclonal antibody directed against the CD22 antigen (20). In vitro immunohistological evaluations demonstrated reactivity of the LL2 antibody with 50 of 51 B-cell NHL specimens tested, but not with other malignancies or normal nonlymphoid tissues (20, 21). Whereas rituximab has been postulated to act through antibody-dependent cellular cytotoxicity (22), complement-mediated cytotoxicity (22), direct induction of apoptosis (23), or other pathways, the mechanism of action of LL2 is still under active investigation (24). Epratuzumab, the humanized (CDR-grafted) IgG1 version of LL2, was developed to reduce the potential for immunogenicity, to prolong half-life, and to increase effector function (25). Preliminary clinical evaluations of this humanized antibody labeled with $^{125}$I and with $^{111}$In/In$^{26}$Y have shown evidence of tumor localization and accumulation, as well as evidence of therapeutic activity for the radioimmunoconjugate (26–28).

Herein we report Phase I/II clinical trial results of epratuzumab in patients with recurrent aggressive NHL, including information on safety, pharmacokinetics, and antilymphoma activity. In this study, epratuzumab was administered by weekly infusion for 4 consecutive weeks at different dose levels. These results demonstrate that single-agent epratuzumab has an excellent safety profile, exhibits antitumor activity, and offers promise as a new agent with potential utility in the treatment of aggressive NHL.

PATIENTS AND METHODS

Study Population

Fifty-six patients with relapsed or refractory aggressive NHL (with at least one prior chemotherapy regimen) were enrolled in this Phase I/II study between April 1998 and November 2000. Patients were required to have CD22+ NHL, as shown by either immunohistochemistry or flow cytometry of malignant tissue obtained at any time point before enrollment. International Working Formulation classification of lymphoma subtype was used at the time of study design and was converted to the World Health Organization classification for this report. At least 4 weeks had elapsed after chemotherapy, radiotherapy, or biological therapy, and 2 weeks had elapsed after corticosteroid use. Additional study eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; serum creatinine of $<1.5 \times$ the upper limits of normal; serum bilirubin of $<1.5 \times$ upper limits of normal; and absence of hepatitis B and C positivity. The protocol was approved by the Weill Medical College of Cornell University and New York Presbyterian Hospital Institutional Review Board, and all patients provided informed consent.

Study Drug Administration

Epratuzumab [humanized IgG1 anti-CD22 monoclonal antibody (hLL2)] was produced and quality-controlled at Immunomedics, Inc. (Morris Plains, NJ) and administered by intravenous infusion at doses of 120, 240, 360, 480, 600, or 1000 mg/m$^2$/week for 4 consecutive weeks.

Dose escalation was sequential, with each dose cohort initiated in the absence of any dose-limiting toxicity (DLT) in the previous group. Because clinical activity was observed at doses of $\geq 240$ mg/m$^2$ without DLT, dose escalation was stopped at 1000 mg/m$^2$, and additional patients were treated at dose levels of $\geq 240$ mg/m$^2$ to further assess efficacy. Before each infusion, patients were premedicated with acetaminophen and diphenhydramine to minimize any potential infusion reactions.

Study Design

The study was an open-label, Phase I/II trial designed to evaluate the safety, pharmacokinetics, and efficacy of epratuzumab therapy. Infusions were administered once weekly for 4 consecutive weeks, with restaging for treatment response performed 4 weeks after the last infusion. Patients were evaluated every 3–4 months for the first 2 years and every 6 months thereafter until disease progression. Adverse events were recorded throughout the study and graded according to the National Cancer Institute (NCI) Common Toxicity Criteria (29). Laboratory assessments (including serum chemistry, complete blood count, immunophenotyping of blood mononuclear cells, urinalysis, and quantitative serum immunoglobulin) were performed at screening, 24 h after the last infusion, and at restaging. Vital signs were monitored every 15 min during the infusions.
Blood samples were tested for the presence of human antihuman antibodies (HAHAs) using an enzyme-linked immunosorbent assay developed by Immunomedics, Inc., which had a lower level of detection of 25 ng/mL. Samples were obtained within 4 weeks before study entry, 24 h after the last infusion, at restaging, and 3–4 months after restaging.

Blood samples to determine serum concentrations of epratuzumab were collected before each weekly infusion, 30 min after the end of each infusion, and periodically thereafter for the next 8 weeks, when possible. More extensive sampling after the fourth infusion sufficient for half-life determination was performed on a subset of patients ($n = 10$).

Study design used ECOG definitions for complete response (CR), partial response (PR), stable disease, and progressive disease (PR). Bidimensional computed tomography data for the neck/chest and abdomen/pelvis were collected at screening, restaging, and follow-up for evaluation of disease response. Bone marrow aspirate and biopsy were performed at study entry and to confirm CR after treatment in patients who had no radiographic or other evidence of disease but had bone marrow involvement at baseline. A range of dose levels was evaluated to identify safe and potentially active doses for use in Phase II clinical trials.

Study End Points

Safety. Safety end points included the incidence of adverse events (including those occurring during or within 7 days of the epratuzumab infusion and all later events deemed possibly or probably treatment-related) and change in HAHAs status, laboratory values, and infusion-day vital signs. DLT was defined as any grade 3 or 4 (according to the NCI Common Toxicity Criteria) treatment-related adverse event. Maximum tolerated dose was defined as the dose level with an observed incidence of DLT in no more than 1 of 6 patients, such that for a given cohort, if 2 of 3 patients or 2 of 6 patients experienced DLTs, the maximum tolerated dose was determined as the dose given in the preceding cohort.

Pharmacokinetics. Serum concentration of epratuzumab was measured at various time intervals using an anti-idiotype-based competitive enzyme-linked immunosorbent assay developed by Immunomedics, Inc. The mean serum half-life of epratuzumab was calculated based on measurements after the last infusion for those subjects having data available from a sufficient number of time points.

Efficacy. Efficacy was evaluated by calculating the OR rate overall and at each dose level (the proportion of patients whose best response at any time during the study was either a CR or PR before disease progression); duration of response was defined as the time from the date a response is determined to the date of first evidence of progression or death regardless of cause; and time to progression (TTP) was defined as the time from study day 1 to the date of first evidence of progression or death, if determined to be due to disease progression.

Statistical Analysis

All patients who received ≥1 dose of epratuzumab were included in the safety analyses. The analyses of OR rate for a given dose and TTP were based on the evaluable patient subset (all enrolled patients who received ≥1 dose of epratuzumab, had a diagnosis of recurrent aggressive NHL, and had ≥1 posttreatment evaluation for response or had withdrawn from study before the first posttreatment evaluation of response due to disease progression). Duration of response was analyzed for the patients who responded within the evaluable subset. The proportion of patients with OR is provided with its 95% confidence interval (CI). Median duration of response and TTP were estimated using the Kaplan-Meier method. Karnofsky performance scores were converted to ECOG performance scores for the analysis.

RESULTS

Patients

Fifty-six patients with aggressive NHL received at least 1 dose of epratuzumab and were included in the evaluation of safety. Fifty-two of these patients were included in the evaluation of efficacy; 4 patients withdrew from the study and were not included in the evaluation of efficacy because of inadequate posttreatment evaluation. Dose escalation was conducted with three patients receiving 120 mg/m² in the initial cohort. Subsequently, three patients per group were treated at each of the 240, 360, 480, and 600 mg/m²/week dose levels, and one patient was treated at the 1000 mg/m² level. Because biological agents do not necessarily have optimal activity at the maximally tolerated dose, additional patients were treated at dose levels (≥240 mg/m²) where clinical activity was observed to assess efficacy. Overall, of the 52 patients assessable for response in the study, 3 patients received 120 mg/m², 7 received the 240-mg/m² dose, 23 subjects received epratuzumab at a weekly dose of 360 mg/m², 11 received 480 mg/m², 7 patients received the 600-mg/m² dose, and 1 received 1000 mg/m². Thirty-three of the 52 patients who were evaluable for both safety and efficacy had DLBCL.

Patient Characteristics

Demographic characteristics for patients included in the analysis of safety are shown in Table 1. More men (63%) than women were enrolled; age ranged from 19 to 88 years, with a median age of 61.0 years. Of the patients with available data ($n = 50$), most (84%) had bulky disease of ≥5 cm, and 63.3% had elevated (>234 units/liter) lactate dehydrogenase levels. Patients had received multiple prior therapies (median, 4 prior therapies; range, 1–11 prior therapies): 58.9% had previously received rituximab; and 25% had received high-dose chemotherapy and stem cell transplant as prior therapy. Thirty-five patients (62.5%) had DLBCL, 9 (16.1%) had MCL, and 12 had other aggressive histologies (such as follicle center cell lymphoma, grade 3 and diffuse follicle center lymphoma, grade 1).

Study End Points

Safety. Ninety-six percent of patients experienced one or more adverse events, with 42% of patients experiencing at least one treatment-related adverse event. All treatment-related events were mild to moderate in severity (Fig. 1). These events occurred principally with the first infusion and were less common thereafter. The most frequent toxicity for all adverse events was fatigue (23%). Other toxicities (whether or not they were...
Table 1. Baseline demographic characteristics for patients receiving at least 1 dose of epratuzumab

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Patients receiving at least 1 dose of epratuzumab (N = 56)</th>
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<tbody>
<tr>
<td>Median age (range) (yrs)</td>
<td>61.0 (19-88)</td>
</tr>
<tr>
<td>No. of females (%)</td>
<td>21 (38)</td>
</tr>
<tr>
<td>Median no. prior therapies (range)</td>
<td>4 (1-11)</td>
</tr>
<tr>
<td>No. with prior rituximab treatment (%)</td>
<td>33 (58.9)</td>
</tr>
<tr>
<td>No. with prior high-dose chemotherapy and stem cell transplant (%)</td>
<td>14 (25)</td>
</tr>
<tr>
<td>Median time from initial diagnosis (range) (mo)</td>
<td>39.5 (3-169)</td>
</tr>
<tr>
<td>WHO classification [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Follicle center cell, follicular grade III</td>
<td>4 (7.1)</td>
</tr>
<tr>
<td>Diffuse follicle center lymphoma, grade I</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Diffuse follicle center lymphoma, grade II</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>DLBCL</td>
<td>35 (62.5)</td>
</tr>
<tr>
<td>MCL</td>
<td>9 (16.1)</td>
</tr>
<tr>
<td>Other (marginal zone)</td>
<td>4 (7.1)</td>
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<tr>
<td>No. with ECOG performance scale = 0 (%)</td>
<td>22 (39.3)</td>
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<tr>
<td>No. with bulky disease at least 5 cm (%)</td>
<td>42 (84)*</td>
</tr>
<tr>
<td>Median SPD (range) (cm²)</td>
<td>32.1 (1.04–202.61)</td>
</tr>
<tr>
<td>No. with LDH &gt; 234 units/liter (%)</td>
<td>31 (55.4)</td>
</tr>
<tr>
<td>Median peripheral blood B-cell counts, CD20, cells/µl (range)</td>
<td>16.6 (0–282.605)*</td>
</tr>
</tbody>
</table>

Abbreviations: WHO, World Health Organization; LDH, lactate dehydrogenase.
* n = 50.
† n = 46.

infusion/treatment-related) included vomiting, dyspnea, nausea, back pain, upper respiratory infection, diarrhea, and cough (Table 2). No clinical correlation between the frequency of adverse events and administered dose level was observed, and no DLT occurred. No clinically significant changes in laboratory measures (including hematology values and immunoglobulin levels) or vital signs were noted, and no serious treatment-related adverse events occurred. Epratuzumab treatment did not affect T-cell levels as measured by CD3+ cell count. B-cell levels, as measured by CD19+ cell counts, were generally low at study entry (median = 16.1 cells/µl at baseline), likely due to prior therapy; therefore, the effects of epratuzumab on circulating B-cell levels could not be assessed in this study. One patient developed transient HAHAS; of note, this patient had an objective CR. Seven patients died within 30 days of their last infusion; six of seven deaths were related to disease progression.

**Pharmacokinetics.** Based on measurements after the last infusion, epratuzumab had a mean serum half-life of 23.9 days (SD, 13.1 days; n = 10), which is comparable to the half-life of a human IgG1 (21 days; Ref. 31).

**Efficacy.** When all dosing groups and histologies are considered, 5 of the 52 evaluable patients (10%; 95% CI, 3–21%) achieved an OR. Three patients (6%; 95% CI, 1–16%) had a CR, one each at the 240-, 360-, and 600-mg/m² dose levels. Two patients (4%; 95% CI, 0–13%) had a PR, one at 240 mg/m² and one at 360 mg/m². Twelve patients (23%; 95% CI, 13–37%) had stable disease as best response, and 35 (67%; 95% CI, 53–80%) progressed. An additional DLBCL patient given 480 mg/m² progressed [increase in the sum of products of greatest diameter (SPD) = 35%] on study day 55 and was included as a nonresponder in the analyses; however, this patient had a PR (decrease in SPD = 73%) on study day 172 and a CR on study day 659 without interim therapy. The duration of response for this patient was 21 months.

Overall, 15% of DLBCL patients had ORs: 2 of 6 (33%), 2 of 13 (15%), and 1 of 5 (20%) patients responded at the 240-, 360-, and 600-mg/m² dose levels, respectively (Fig. 2). No responses were observed at the 480- and 1000-mg/m² dose levels (n = 8 and n = 1, respectively). Three of the five responses were complete, and by ECOG response criteria, they were confirmed at ≥4 weeks after the first determination of response (30). No patient who was classified as having a CR had residual nodal lesions of ≥1 cm² in bidimensional measurements. Overall, 11 (20%) patients (all histologies) experienced some tumor mass reduction (Fig. 3). By Kaplan-Meier estimate, the median duration of OR is 26.3 weeks (range, 11.1–219.9+ weeks), and the median TTP for responding patients is 35.0 weeks (range, 20.9–225.7+ weeks). Biopsies were not routinely performed at progression after epratuzumab because this procedure was not prospectively included in the protocol. Interestingly, however, one responder (with multiple prior biopsies demonstrating DLBCL) was found to have progression with marginal zone lymphoma after epratuzumab. Two responses are ongoing at ≥34 months, including one patient with rituximab-refractory disease.

**DISCUSSION**

Unlabeled monoclonal antibody therapy of lymphomas has been under evaluation for more than two decades, focusing mostly on antibodies that target the CD19, CD20, and CD52...
antigens associated with B-cell malignancies (32–36). In 1980, Nadler et al. (37, 38) showed that a murine monoclonal antibody could target human lymphoma cells and induce tumor cell death. Lymphoma regressions were observed by Hsu et al. (39) after treatment with tumor-specific anti-idiotype antibodies. Subsequent therapeutic approaches evaluated antibodies directed against B-cell lineage antigens widely associated with B-cell malignancies, with Press et al. (40) demonstrating evidence of activity with a murine antibody targeting CD20. The most significant recent advance in the clinical care of lymphoma patients, however, has been the development of the chimeric anti-CD20 monoclonal antibody rituximab, an antibody approved by the United States Food and Drug Administration for the treatment of indolent NHL.

Although the single-agent activity of rituximab is most prominent in low-grade lymphomas, its predominant use in aggressive NHL subtypes is in combination with chemotherapy, particularly CHOP (12). Despite the demonstrated benefits of rituximab in this patient population, approximately half of patients with DLBCL die of their disease, indicating that new agents are needed. One strategy is the development of non-cross-reactive antibodies targeting other B-cell antigens, which may have different and nonoverlapping mechanism(s) of antitumor activity. Treatment with a combination of a non-cross-reactive antibody and rituximab (and/or chemotherapy) might result in higher antitumor activity than either of the drugs alone. Antibodies targeting the CD19 or CD52 antigens have been tested in B-cell malignancies in general, but clinical benefit with these approaches has not been well established to date in aggressive NHL (32, 41).

The wide expression of CD22 in B-cell malignancies (15), including aggressive lymphoma, and its role in B-cell biology make it a potentially useful target for immunotherapy of aggressive NHL. Previous studies have evaluated murine and humanized forms of an anti-CD22 antibody both preclinically and clinically, as a carrier of radionuclides for NHL imaging and therapy (42–44), as well as a conjugate with toxins [ricin (45–47), pseudomonas exotoxin (48), or RNase (49)] for therapy. Results of these trials with one radioimmunoconjugate form of the antibody (42, 43) suggested that the unlabeled

### Table 2

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Weekly dose group (mg/m²)</th>
<th>Total*</th>
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<tbody>
<tr>
<td></td>
<td>120 (n = 3)</td>
<td>55 (98)</td>
</tr>
<tr>
<td>No. of patients with adverse events</td>
<td>240 (n = 9)</td>
<td>13 (23)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>360 (n = 24)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>480 (n = 12)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Nausea</td>
<td>600 (n = 7)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1000 (n = 1)</td>
<td>6 (11)</td>
</tr>
</tbody>
</table>

* Intention to treat subset includes all subjects receiving at least one dose of study drug.

**Note.** All values expressed as n (%).

**Fig. 2** OR rates by dose for evaluable patients with DLBCL. n = number of evaluable patients. □, PR; ■, CR.
murine antibody had some antilymphoma activity and prompted the development of the humanized form (25) of the naked antibody and its clinical evaluation. Results in patients with indolent NHL showed evidence of both safety and activity in patients with NHL who had progressive disease after numerous prior therapies, including rituximab (50). In aggressive NHL, development of an unlabeled antibody (rather than radiolabeled agents) may be of particular importance because naked antibodies are generally easier to combine with the chemotherapy agents usually required for disease control, as opposed to indolent NHL, where single agents are commonly used to minimize toxicity.

This trial is the first clinical evaluation of the safety and efficacy of this anti-CD22 humanized monoclonal antibody, epratuzumab, in the treatment of patients with aggressive NHL. It was designed to assess the safety, pharmacokinetics, and efficacy of weekly administration of epratuzumab for 4 weeks and to define dosing regimens for further clinical development. Our findings indicate that epratuzumab has an excellent safety profile, with mostly grade 1 toxicities that were principally associated with the first infusion. Side effects were not related to protein dose amount, which is particularly notable given that the vast majority of infusions were completed in 60 min or less. No effects on hematological parameters, immunoglobulin levels, or serum chemistries were observed. Because of relatively low baseline levels (likely related to previous therapy), direct effects of epratuzumab on circulating B-cell levels could not be clearly determined in this study. Of note, evaluation of epratuzumab in a different population of patients (indolent NHL) indicates that epratuzumab administration can result in decreases in number of circulating B cells (50), and treatment of normal nonhuman primates has yielded similar findings (51).

It is interesting that across all doses and histologies, 20% of patients demonstrated evidence of some level of antilymphoma activity as measured by reduction in tumor mass. This occurred despite the extensive previous therapy in this group (group members had a median of four previous regimens, reflecting a poor prognosis group). Fifteen percent of subjects with DLBCL demonstrated ORs (three of five were complete), and an additional patient (classified as a nonresponder) had initial disease progression followed by a delayed CR without intervening treatment. This individual had an increase in SPD of 35% at approximately 2 months on study, had a PR (decrease in SPD/100 months) at approximately 6 months, and a CR at nearly 2 years. The time course of this patient’s response, unusual in this disease setting even with cytotoxic drugs, leads us to speculate

### Table 3  Baseline characteristics by response for evaluable patients (N = 52)

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Responders (n = 5)</th>
<th>Nonresponders (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range) (yrs)</td>
<td>59.0 (45–81)</td>
<td>62.0 (19–88)</td>
</tr>
<tr>
<td>No. of females (%)</td>
<td>3 (60.0)</td>
<td>17 (36.2)</td>
</tr>
<tr>
<td>Median no. of prior chemotherapies (range)</td>
<td>3 (2, 5)</td>
<td>3 (1, 9)</td>
</tr>
<tr>
<td>Median no. of prior radiotherapies (range)</td>
<td>1 (0, 2)</td>
<td>1 (0, 4)</td>
</tr>
<tr>
<td>No. with prior rituximab treatment (%)</td>
<td>3 (60.0)</td>
<td>29 (61.7)</td>
</tr>
<tr>
<td>No. with prior high-dose chemotherapy and stem cell transplant (%)</td>
<td>3 (60.0)</td>
<td>11 (23.4)</td>
</tr>
<tr>
<td>Median time from initial diagnosis (range) (mo)</td>
<td>46.7 (21–78)</td>
<td>40.9 (3–169)</td>
</tr>
<tr>
<td>WHO classification [n (%)]</td>
<td></td>
<td></td>
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<tr>
<td>Follicle center cell, follicular grade III</td>
<td>0 (0.0)</td>
<td>3 (6.4)</td>
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<td>Diffuse follicle center lymphoma, grade I</td>
<td>0 (0.0)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Diffuse follicle center lymphoma, grade II</td>
<td>0 (0.0)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>DLBCL</td>
<td>5 (100.0)</td>
<td>28 (59.6)</td>
</tr>
<tr>
<td>MCL</td>
<td>0 (0.0)</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>Other (marginal zone)</td>
<td>0 (0.0)</td>
<td>3 (6.4)</td>
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<tr>
<td>No. with ECOG performance scale = 0 (%)</td>
<td>4 (80.0)</td>
<td>17 (36.2)</td>
</tr>
<tr>
<td>No. with bulky disease at least 5 cm (%)</td>
<td>2 (40.0)</td>
<td>36 (76.6)</td>
</tr>
<tr>
<td>Median SPD (range) (cm²)</td>
<td>13.39 (1.80–30.19)</td>
<td>34.86 (1.04–202.61)</td>
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<tr>
<td>No. with LDH &gt; 234 units/liter (%)</td>
<td>4 (80.0)</td>
<td>23 (48.9)</td>
</tr>
<tr>
<td>Median peripheral blood B-cell counts, CD20, cells/µl (range)</td>
<td>12.2 (3–54)</td>
<td>16.6 (0–282.605)*</td>
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Abbreviation: WHO, World Health Organization; LDH, lactate dehydrogenase.

* n = 38.
that immune mechanisms may play a role in the antilymphoma effects of epratuzumab, as with other monoclonal antibodies.

Of note in multiply relapsed DLBCL, two CRs are ongoing at ≥34 months after therapy. Most responding patients had either progressed after high-dose chemotherapy and ASCT (three of five patients) or were ineligible for ASCT (1 patient who was >80 years old). Although this group represents patients with limited therapeutic alternatives, they have been reported to respond well to single-agent rituximab therapy with an OR rate of 53% and a median progression-free survival of 13 months (range, 6–18 months; Ref. 11). The clinical activity of epratuzumab in aggressive NHL was limited to the DLBCL subtype in this study; however, this group represented most patients enrolled, and insufficient numbers of patients with other histologies were evaluated to fully assess activity in other NHL subtypes. Responses were seen at doses ranging from 240 to 600 mg/m², but no clear dose-response relationship was observed. This result reflects the relatively small number of patients treated at each dose level and is consistent with findings in patients with indolent NHL, in which clinical responses appear to be higher at the 360-mg/m²/week (five of nine patients) or were ineligible for ASCT (1 patient [three of five patients]) or were ineligible for ASCT (1 patient).

The precise mechanism of action of epratuzumab has not been defined but may relate to effects on B-cell signaling (through induction of C/EBPα phosphorylation). Ligation of human CD22 with monoclonal antibodies (or natural ligands) triggers internalization of the complex, tyrosine phosphorylation of the cytoplasmic tail of CD22, and binding of the tyrosine phosphatase SHP-1, a negative regulator of signaling from the B-cell receptor. As a consequence in resting B cells, CD22 engagement negatively regulates BCR signaling. Of note, engagement of CD22 in activated B cells results (paradoxically) in up-regulation of BCR signaling (16). With respect to the mechanism of action of epratuzumab, it is possible that inappropriate signaling and interference with CD22 signaling due to antibody binding may render cells more prone to apoptosis (24). Additionally, a recent report suggested that antibody-dependent cellular cytotoxicity activity was involved in the antitumor activity of epratuzumab in preclinical models, and it was also shown that, in these models, epratuzumab can enhance the efficacy of rituximab when the two antibodies are combined (52–54). This appears in support of preliminary clinical observations that in low-grade follicular and DLBCL histologies (55), the combination of epratuzumab with rituximab could potentially offer greater therapeutic effects than either agent given alone, reflected by an apparent improvement in the CR rate. The demonstration of CRs in DLBCL in this Phase I/II study with single-agent epratuzumab supports further evaluation of this antibody combination. Ongoing studies include evaluation of epratuzumab in combination with CHOP-rituximab in first-line treatment of DLBCL.

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Epratuzumab in Aggressive NHL


Epratuzumab, a Humanized Anti-CD22 Antibody, in Aggressive Non-Hodgkin’s Lymphoma: Phase I/II Clinical Trial Results

John P. Leonard, Morton Coleman, Jamie C. Ketas, et al.


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