Cure of Disseminated Human Lymphoma with [177Lu]Lu-Ofatumumab in a Preclinical Model

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Although immunotherapies that target CD20 on most non-Hodgkin lymphoma (NHL) cells have improved patient outcomes, current therapies are inadequate because many cases are, or become, refractory or undergo relapse. Here, we labelled the third-generation human anti-CD20 antibody ofatumumab with [177Lu], determined the in vitro characteristics of [177Lu]-ofatumumab, estimated human dosimetry, and assayed tumor targeting and therapeutic efficacy in a murine model of disseminated NHL.

Methods: CHX-A^-diethylenetriaminepentaacetic acid-[177Lu]-ofatumumab was prepared. We evaluated radiochemical yield, purity, in vitro immunoreactivity, stability, (n = 7), affinity, and killing of CD20-expressing Raji cells (n = 3). Human dosimetry was estimated from biodistribution studies as percentage injected activity per gram using C57BL/6N mice. Tissue and organ biodistribution was determined in R2G2 immunodeficient mice with subcutaneous Raji-cell tumors. Therapy studies used R2G2 mice with disseminated human Raji-luc tumor cells (n = 10 mice/group). Four days after cell injection, the mice were left untreated or were treated with ofatumumab, 8.51 MBq of [177Lu]-IgG, or 0.74 or 8.51 MBq of [177Lu]-ofatumumab.

Results: Radiochemical yield was 93% ± 2%, radiochemical purity was 99% ± 1%, and specific activity was 401 ± 17 MBq/mg. Immunoreactivity was substantially preserved, and more than 75% of [177Lu] remained che- lated after 7 d in serum. [177Lu]-ofatumumab specifically killed Raji- luc cells in vitro (P < 0.05). Dosimetry estimated that an effective dose for human administration is 0.36 mSv/MBq and that marrow may be the dose-limiting organ. Biodistribution in subcutaneous tumors 1, 3, and 7 d after [177Lu]-ofatumumab injection was 11, 15, and 14 percentage injected activity per gram, respectively. In the therapy study, median survival of untreated mice was 19 d, not statistically different from mice treated with 8.51 MBq of [177Lu]-IgG (25 d). Unlabeled ofatumumab increased survival to 46 d, similar to 0.74 MBq of [177Lu]-ofatumumab (59 d), with both being superior to no treatment (P < 0.0003). Weight loss and increased tumor burden preceded death or killing of the animal for cause. In contrast, treatment with 8.51 MBq of [177Lu]-ofatumumab dramatically increased median survival (>221 d), permitted weight gain, eliminated detectable tumors, and was curative in 9 of 10 mice.

Conclusion: [177Lu]-ofatumumab shows favorable in vitro characteristics, localizes to tumors, and demonstrates curative therapeutic efficacy in a disseminated lymphoma model, showing potential for clinical translation to treat NHL.

Key Words: CD20; lymphoma; targeted β-particle therapy; radioimmunotherapy; lutetium

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on average, with an average tissue range of 220 μm. Emission of low-abundance γ-particles by 177Lu permits imaging by SPECT.

Recently, ofatumumab, a third-generation anti-CD20 fully human antibody, was developed. Ofatumumab is a type I antibody that is internalized after CD20 binding (8). We showed by biodistribution and PET imaging studies that [89Zr]Zr-DFO-ofatumumab targets CD20-positive subcutaneous xenograft tumors as well as [86Rb]Rb-DFO-rituximab (9).

Here, we describe the synthesis and evaluation of [177Lu]Lu-ofatumumab. We present in vitro characteristics, dosimetry estimation, and subcutaneous tumor targeting. We also show that [177Lu]Lu-ofatumumab therapy results in long-term survival and elimination of tumor cells in a murine model of disseminated human lymphoma.

**MATERIALS AND METHODS**

**Reagents and Cells Culture**

Ofatumumab (IgG1 κ; Novartis) was purchased from the Washington University clinical pharmacy, and human IgG1 κ was purchased from BioXcel. Raji cells and Raji-luc cells stably expressing luciferase (10) were cultured as previously described (9). SCN-CHX-A′′′-DTPA ([(R)-2-amino-3-(4 isothiocyanatophenyl)propyl]-trans(S,S)-cyclohexan-1,2-diamine-pentaacetic acid) was from Macrocyclics, size-exclusion chromatography columns from Fisher Scientific, and α-luciferin from GoldBio. Sigma provided human serum, sodium acetate, diethylaminoethylamine tetraacetic, tetrathylenammonium acetate, and l-sodium ascorbate. 177Lu from the University of Missouri was dissolved in 0.2 M HCl. Silica gel thin-layer chromatography paper was from Agilent, and the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) salt assay was from Promega.

**Antibody Conjugation, Radiolabeling, Thin-Layer Chromatography, Mass Spectrometry, and Fast-Performance Liquid Chromatography**

Antibody was incubated with SCN-CHX-A′′′-DTPA in 0.1 M sodium carbonate, pH 9.0, at a chelator-to-antibody molar ratio of 8.1:1 for 1 h at 37°C and purified by size-exclusion chromatography into 0.5 M NH4OAc, pH 7.0. A 477-MBq quantity of 177Lu was added to 400 μg of CHX-A′′′-DTPA-antibody with 20 mM 0.1 M NaOAc, pH 7.0. After 2 h at 37°C, DTPA was added to 1.5 M sodium final concentration, followed by size-exclusion chromatography purification into saline and the addition of a 10 mg/mL concentration of l-sodium ascorbate. Thin-layer chromatography and fast-performance liquid chromatography were done as previously described (9). Radiochemical yield was assayed with a CRC55-tW dose calibrator. Chelate number was determined using a Fisher Scientific Exactive Plus EMR mass spectrometer operating at a mass (m/z)-to-charge (z) range from 800 to 12,000 and a resolving power of 8,750 or 17,500 at 543 m/z.

**Serum Stability, Immunoreactivity, In Vitro Stability, Affinity, and Cell Killing Assays**

To assay stability, 14.8 MBq of [177Lu]Lu-ofatumumab or 177Lu were added to 10% human serum in 20 mM NaOAc 150 mM NaCl pH 7.0 with 10 mg/mL L-SA and incubated at 37°C. Another aliquot of [177Lu]Lu-ofatumumab was incubated at 4°C in buffer without serum and with 10 mg/mL L-SA. Aliquots were analyzed by thin-layer chromatography at 0, 1, 5, and 7 d. Immunoreactivity was assayed as previously described (9). To assay affinity, 2.5 × 10⁹ Raji cells without or with 10 μg of ofatumumab were incubated with [177Lu]Lu-ofatumumab, washed after 4 h at 23°C, and γ-counted. To assay cell killing, 2 × 10⁹ Raji-luc cells in 1 mL of RPMI medium with 10% heat-treated fetal bovine serum were exposed to no treatment, ofatumumab, [177Lu]Lu-IgG, or [177Lu]Lu-ofatumumab, with cognate unlabeled antibody added to 20 μg total. After 14 h at 37°C, the cells were washed and 20% were resuspended in fresh medium for an additional 168 h followed by MTS assay.

**Biodistribution of [177Lu]Lu-Ofatumumab in Mice with Subcutaneous Raji Tumors**

The Washington University in St. Louis Animal Care and Use Committee approved the animal studies. Biodistribution with tumor-bearing mice used female 6- to 8-week-old immunodeficient Rag2-IL2rg (R2G2, B6;129-Rag2tm1Gwe/Luc3.1/B6;129-Rag2tm1FwaII2rgtm1Rsky/Dw1Hsd) mice (Envigo) injected subcutaneously with 5 × 10⁶ Raji-luc cells. Mice with palpable tumors were injected intravenously with 10–20 μg of [177Lu]Lu-ofatumumab and killed 1, 3, or 7 d later. Distribution was calculated as decay-corrected percentage injected activity per gram (%IA/g) using a Beckman 8000 γ-counter and a 1- to 500-kV window.

**Dosimetry Estimation**

Naïve 5- to 6-week-old C57Bl6/N mice injected intravenously with 370 kBq (10 μg) of [177Lu]Lu-ofatumumab were killed 4 h, 1 d, 2 d, 5 d, or 11 d later, and tissue and organs were γ-counted. Bone was counted after marrow separation. Urine and feces were collected at 4 h, 1, 2 d, and 2 d. Organ residence times were calculated by analytic integration of single or multieponential fits of the time–activity curve and scaled to human

**TABLE 1**

<table>
<thead>
<tr>
<th>Organ</th>
<th>mSv/MBq</th>
<th>rad/mCi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>0.39</td>
<td>1.44</td>
</tr>
<tr>
<td>Brain</td>
<td>0.05</td>
<td>0.19</td>
</tr>
<tr>
<td>Breasts</td>
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<td>0.91</td>
</tr>
<tr>
<td>Esophagus</td>
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<td>0.96</td>
</tr>
<tr>
<td>Eyes</td>
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<td>0.91</td>
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<td>1.34</td>
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<td>Small intestine</td>
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<tr>
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<tr>
<td>Right colon</td>
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<td>0.97</td>
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<td>Thyroid</td>
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<tr>
<td>Uterus</td>
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</tr>
<tr>
<td>Total body</td>
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<tr>
<td>Effective dose (mGy/MBq; rem/mCi)</td>
<td>0.36</td>
<td>1.34</td>
</tr>
</tbody>
</table>
organ weight by relative organ mass scaling (1/1), which was not applied
to the gastrointestinal tract organs. To estimate human radiation dose, re-
dence times were entered into OLINDA, version 2.2, using the MIRD
adult-female model and organ weights from International Commission on
Radiological Protection publication 106 (12). The calculated radiation
dose includes contributions from β- and γ-rays from 177Lu within the
organ, neighboring organs, and remainder of the body.

Therapeutic Studies, Mouse Weight, and
Bioluminescent Imaging

R2G2 mice (10 per group) injected intravenously with 1 × 10⁶
Raji-luc cells and either left untreated or injected 4 d later with ofatu-
mumab, [177Lu]Lu-IgG, or [177Lu]Lu-ofatumumab. When used, 20 μg
of antibody were injected per mouse. Bioluminescent images were
acquired as previously described (13). Mice were killed if they experi-
enced hind-limb paralysis, lost more than 20% of their body weight,
or had other signs of morbidity.

Statistics

Statistical analyses used Prism software (version 9.0; GraphPad).

RESULTS

Synthesis of [177Lu]Lu-Ofatumumab and Radiochemical Yield,
Purity, and Immunoreactivity

SCN-CHX-A’’-DTPA was conjugated to ofatumumab and puri-
ified. Mass spectrometry indicated an average of 3.2 chelators per
antibody. After 177Lu radiolabeling, [177Lu]Lu-ofatumumab was
purified (n = 7). Radiochemical purity was more than 99% ± 1%,
radiochemical yield was 93% ± 2%, and specific activity was
401 ± 17 MBq/mg. Immunoreactivity was 49% ± 3% and 2% ± 1%
1% after blocking with unlabelled ofatumumab.

Serum Stability, In Vitro Cell Killing, and Affinity of
[177Lu]Lu-Ofatumumab

After 7 d, over 90% of 177Lu remained chelated in buffer at 4°C, and
over 75% remained chelated in human serum at 37°C (Supplemental
Fig. 1A; supplemental materials are available at http://jnm.snmjournals.org). Targeting and
killing of CD20-expressing cells were assayed (Supplemental Fig. 1B) by adding either
no antibody or [177Lu]Lu-ofatumumab or [177Lu]Lu-IgG (0.74–11.10
MBq/mL) to Raji-luc cells; incubating for 14 h; changing
the medium; and, 168 h later, determining cell
viability. Compared with no antibody, [177Lu]Lu-IgG showed no cell killing at any
dose. [177Lu]Lu-ofatumumab at 3.7 MBq/mL or higher showed dose-dependent killing com-
pared with no antibody and [177Lu]Lu-IgG
(P < 0.05, n = 3). [177Lu]Lu-ofatumumab showed a 4.3 nM dissociation constant for
CD20 (Supplemental Fig. 1C), consistent with
that noted previously (as described for F2 by
Teeling et al. (14)).

Biodistribution of [177Lu]Lu-Ofatumumab in C57Bl6/N Mice and Estimation of
Human Dosimetry

[177Lu]Lu-ofatumumab biodistribution was determined in C57Bl6/N mice 4 h, 1 d, 2 d, 7
d, and 11 d after injection (Supplemental
Table 1) as %IA/g. Blood %IA/g was 38% at
4 h and 19% after 11 d. Bone distribution
was less than 4%, indicating stable chelation because free 177Lu is a
bone-seeking radionuclide (15). Liver was 9 %IA at 4 h and 5 %IA/g
at 11 d, and marrow was 14 %IA at 4 h and 9 %IA/g at 11 d. Spleen
was 8–9 %IA/g. Approximately 13% of the injected activity was
excreted.

To estimate human dosimetry, integrated time–activity curves for
[177Lu]Lu-ofatumumab were calculated (Supplemental Table 2). The
longest (59.7 h) was in the blood, with extended time–activity curves
seen in the blood-rich heart cavity, lung, and liver. Because of its
large mass, muscle had the second longest time–activity curve, at
39 h. The adult human female model (Table 1) showed estimated
dosimetry of 0.2–0.5 mSv/MBq in most organs, with the largest dose
being to the heart wall (1.02 mSv/MBq) and lesser doses found for
liver, spleen, and kidney (0.36, 0.48, and 0.43 mSv/MBq, respec-
tively). Estimated doses to the osteogenic cells (bone surfaces) and
red marrow were 0.82 and 0.54 mSv/MBq, respectively. The esti-
imated effective dose was 0.36 mSv/MBq.

Biodistribution of [177Lu]Lu-Ofatumumab in Mice with
Subcutaneous Raji-Cell Tumors

Biodistribution was investigated in R2G2 mice with subcutane-
ous Raji-cell tumors (Fig. 1). These mice are proficient in double-
strand DNA-break repair and are less likely to show artifactual
radiation toxicity than are repair-deficient PrkdcSCID mice (16).
[177Lu]Lu-ofatumumab was injected at a low activity (370–444
kBq) to limit therapeutic effect, and biodistribution was deter-
mined 1, 3, and 7 d later (3–16 mice per time point). Blood
decreased from about 13 to 6 %IA/g, with a similar splenic distri-
bution. Liver levels were about 5%, and marrow was 10 %IA at
1 d and 5 %IA/g at 7 d. Bone distribution was 2–3 %IA/g. Tumor
targeting was 11, 15, and 14 %IA/g at 1, 3, and 7 d, respectively.

Murine Therapy Study

To evaluate [177Lu]Lu-ofatumumab therapeutic efficacy, R2G2
mice were injected intravenously with Raji-luc cells, and tumor

![Figure 1](https://example.com/figure1.png)

**FIGURE 1.** [177Lu]Lu-ofatumumab biodistribution in R2G2 mice with subcutaneous Raji tumors. Biodistribution was assayed 1, 3, or 7 d after radiopharmaceutical injection (3–16 mice per time point), with data presented as mean ± SD. One-way ANOVA compares distribution in organ or tis-
sue at each time point. *P < 0.05, **P < 0.001, ***P < 0.0001. Sm Int = small intestine; U Lg Int = upper large intestine; L Lg Int = lower large intestine.
cells were quantified by bioluminescent imaging (13). After injection, these cells disseminate to many organs (10,13,17,18), with hind-limb paralysis being a typical cause for killing of the animal due to growth in and around the spine.

Four days after cell injection, the mice either were left untreated or were treated with native ofatumumab, 8.51 MBq of [177Lu]Lu-human IgG1 (34.5 ± 27 MBq/kg), 0.74 MBq (30 ± 22 MBq/kg) of [177Lu]Lu-ofatumumab, or 8.51 MBq (34.5 ± 25.1 MBq/kg) of [177Lu]Lu-ofatumumab (10 mice per group). Survival (Fig. 2), weight (Supplemental Fig. 2), and bioluminescence (Fig. 3A) were tracked for 221 d. Representative bioluminescent images at selected time points are shown in Figure 3B, and images of all mice just before they died or were killed for cause or study termination are shown in Figure 4.

The median survival of untreated mice was 19 d, with none surviving beyond 22 d. Unlabeled ofatumumab yielded a median survival of 46 d, superior to untreated mice (Mantel–Cox, P < 0.0001), with 1 mouse surviving without weight loss or increased bioluminescence. An 8.51-MBq dose of [177Lu]Lu-IgG yielded 0 of 10 surviving mice and a median survival of 25 d, which was not different from that of untreated mice. For all 3 groups, increased bioluminescence and weight loss occurred before death or killing for cause.

A 0.74-MBq dose of [177Lu]Lu-ofatumumab yielded median survival of 59 d (9/10 mice not surviving), with increased bioluminescence and weight loss before death or killing for cause. This survival was superior to that of untreated mice (Mantel–Cox, P < 0.0001) but not to that of mice receiving treatment with unlabeled ofatumumab. Hind-limb paralysis was frequently associated with death or killing for cause (Supplemental Table 3).

Notable therapeutic efficacy resulted from treatment with 8.51 MBq of [177Lu]Lu-ofatumumab, with 9 of 10 mice surviving with continuous low bioluminescence (Figs. 3 and 4). This survival was greater than that of untreated mice and of mice treated with unlabeled ofatumumab, 8.51 MBq of [177Lu]Lu-IgG, or 0.74 MBq of [177Lu]Lu-ofatumumab (Mantel–Cox, P < 0.0003 for all comparisons). One mouse succumbed at 117 d, but this death appeared unrelated to tumor burden or therapy as no weight loss or increased bioluminescence occurred. Surviving mice displayed weight loss from 10 to 35 d after cell injection but recovered and gained weight.

To determine how quickly therapy affected tumor cells, bioluminescence slopes from 1 to 18 d after initiation of therapy were compared (Fig. 5; Supplemental Fig. 3). Compared with no treatment, ofatumumab, 8.51 MBq of [177Lu]Lu-IgG, and 0.74 MBq of [177Lu]Lu-ofatumumab slowed, but did not eliminate, tumor-cell proliferation. In contrast, 8.51 MBq of [177Lu]Lu-ofatumumab quickly eliminated tumor cells, a finding that was significant compared with no treatment, treatment with unlabeled ofatumumab, treatment with 8.51 MBq of [177Lu]Lu-IgG, or treatment with 0.75 MBq of [177Lu]Lu-ofatumumab (P < 0.05).

**FIGURE 2.** Survival analysis of mice with disseminated Raji-luc cells with therapy initiated 4 d after cell injection. Kaplan–Meier graph shows median survival, in days. Ofa = ofatumumab.

**FIGURE 3.** Tumor burden of mice with disseminated Raji-luc cells with therapy initiated 4 d after cell injection. (A) Bioluminescence (10 mice per group). (B) Representative bioluminescence images at indicated days after cell injection. Radiance is photons/second/cm²/steradian. Ofa = ofatumumab.
progressing disease, we evaluated [177Lu]Lu-ofatumumab therapy for broad applicability in radiotherapy of cancer. In a model of rapidly progressing disease, we evaluated [177Lu]Lu-ofatumumab displayed curative efficacy. A single 8.51-MBq dose of [177Lu]Lu-ofatumumab due to cross reactivity with normal CD20-positive cells, our dosimetry data provide guidance for activity administration to humans. Dosimetric estimation could also be potentially obtained using a PET imaging surrogate, such as [90Zr]Zr-ofatumumab.

The stable in vivo chelation of 177Lu by CHX-A'-DTPA-ofatumumab agrees with the results of others using this chelator-radionuclide combination (23,24). Although it has been suggested that, for stable 177Lu chelation, macrocyclic DOTA requires high temperatures incompatible with maintaining antibody function (24,25), experiments show that this is not the case (26,27). Thus, CHX-A'-DTPA and DOTA both appear practical for chelation of 177Lu to antibodies and antibody fragments.

Others have used [177Lu]Lu-anti-CD20 intact antibodies or 177Lu-labeled antibody–based radiopharmaceuticals for preclinical and clinical therapy. Ertveld et al. (23), using a single-domain anti-CD20 antibody in immunocompetent mice with CD20-expressing subcutaneous tumors, found a modest therapeutic effect at 140 MBq/mouse; 50 MBq/mouse induced expression of proinflammatory genes, whereas 140 MBq/mouse increased the percentage in the tumor of PD-L1-positive myeloid cells and alternatively activated macrophages. Krasnij et al. (28) compared a single-domain anti-CD20 antibody with unlabeled rituximab and [177Lu]Lu-CHX-A'-DTPA-rituximab in mice with CD20-expressing subcutaneous tumors. All treatments increased survival over no treatment, but [177Lu]Lu-CHX-A'-DTPA-rituximab was only slightly better than rituximab. In a phase I/II study of [177Lu]Lu-DOTA-rituximab in 31 patients with relapsed or refractory CD20-positive lymphoma, mainly hematologic toxicity was observed, with frequent tumor responses and 8 of 11 patients with follicular lymphoma alive after an 84-mo median follow-up (29).

A major finding of the current study is that high therapeutic efficacy of [177Lu]Lu-ofatumumab in a murine model of disseminated lymphoma. Therapy was initiated 4 d after intravenous cell injection, when tumor cells are present individually or as small groups, comparable to micrometastatic or minimal residual disease in humans. An 8.51-MBq dose of [177Lu]Lu-ofatumumab reduced tumor burden within about 2 d and eliminated bioluminescence-detectable tumors, with 9 of 10 mice still alive 221 d later. This response was dose-dependent and specific, as 0.74 MBq of [177Lu]Lu-ofatumumab and 8.51 MBq of [177Lu]Lu-IgG did not extend survival or prevent tumor-cell proliferation. Although attenuation from tissue, skin, and fur means that bioluminescent imaging may not detect a low tumor-cell burden (13), the durability of the response suggests complete elimination of tumor cells by 8.51 MBq of [177Lu]Lu-ofatumumab. After initial weight loss, these mice gained weight, suggesting no or low whole-body toxicity. The internalization of ofatumumab after CD20 binding (30) and the residualization of 177Lu within the cell may contribute to its therapeutic efficacy. Moreover, the lack of murine sequences in [177Lu]Lu-ofatumumab suggests a potential for fractionated therapy or repeated treatments. In an interesting approach, with relatively small subcutaneous tumors of rituximab-resistant Raji cells, Malenge et al. (26) combined [177Lu]Lu-lilotomab (anti-CD37) and unlabeled rituximab, with good therapeutic results.

**DISCUSSION**

Our preclinical studies add to prior work demonstrating the potential of radiolabeled anti-CD20 antibodies to treat NHL. We show that [177Lu]Lu-ofatumumab can be produced with high radiochemical yield and purity, excellent affinity, good stability and immunoreactivity, and potent cell killing. Additional advances include using a fully human anti-CD20 and 177Lu, which have broad applicability in radiotherapy of cancer. In a model of rapidly progressing disease, we evaluated [177Lu]Lu-ofatumumab therapy using dose-response studies and bioluminescence monitoring of tumor-cell burden. A single 8.51-MBq dose of [177Lu]Lu-ofatumumab displayed curative efficacy.

Human dosimetry estimates predict that the highest dose from 177Lu-ofatumumab (1.02 mSv/MBq) will be to the heart wall. The relatively radiation-resistant liver and spleen showed 0.36 and 0.48 mSv/MBq, respectively. The predicted dose to red marrow is 0.54 mSv/MBq, and hematologic toxicity likely will be dose limiting in clinical use, as was found with Bexxar, Zevalin, [177Lu]Lu-I591 (19), [177Lu]Lu-G250 anti-CAIX (20), and [177Lu]Lu-rituximab (21). As 2 Sv is a typical maximal dose for acceptable hematologic toxicity without stem cell support, delivering this radiation to the marrow would be tolerable. As there may be patient-to-patient variability with [177Lu]Lu-ofatumumab due to cross reactivity with normal CD20-positive cells, our dosimetry data provide guidance for activity administration to humans. Dosimetric estimation could also be obtained using a PET imaging surrogate, such as [90Zr]Zr-ofatumumab.

**FIGURE 4.** Bioluminescence images of untreated or treated mice with disseminated Raji-luc cells on final imaging event before mice were killed for cause or study termination. Ofa = ofatumumab.

**FIGURE 5.** Tumor-cell growth in mice 1–18 d after initiation of therapy. Log of slopes of radiance (photons/cm²/steradian) over this time are shown as mean ± SD and were analyzed by ANOVA, comparing all samples with each other (10 mice per group). *P < 0.05. **P < 0.005. ***P < 0.0001. Ofa = ofatumumab.
α-particle therapy is another potential approach to treating lymphoma. Using a murine Raji-cell disseminated lymphoma model, [213Bi]Bi-rituximab (t1/2, 45.6 min) was typically curative when tumor burden was low (4 d after cell injection) but not when it was higher (>8), perhaps because of lack of time to target larger tumor masses before decay. Similarly, [149Tb]Tb-rituximab (t1/2, 4.2 h) therapy initiated 2 d after Daudi-cell intravenous injection increased survival (31). A 175F anti-CD20 antibody with chelated 

**DISCLOSURE**

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