The clinical trial described in our article "Yttrium-90-Labeled Anti-CD20 Monoclonal Antibody Therapy of Recurrent B-cell Lymphoma" (1) built on the work of many investigators' contributions to both preclinical and early clinical studies demonstrating that radioimmunotherapy was a promising new therapeutic approach for the treatment of B-cell lymphoma and that CD20 was a particularly good target. We reported the results of a phase I/II dose escalation study of Yttrium-90 90Y-murine anti-CD20 mAb in patients with recurrent B-cell lymphoma. This was one of the first clinical studies, based on preclinical work (2), to demonstrate that the preinfusion of unlabeled antibody favorably affected the biodistribution of radiolabeled anti-CD20 mAb by decreasing the estimated dose to spleen by approximately 4-fold and increasing the mean projected tumor dose from 16.5 to 40.3 cGy/mCi. The improved biodistribution of the radiolabeled antibody following administration of unlabeled antibody was presumably due, at least in part, to decreased nonspecific uptake of antibody by cells with Fc receptors in the reticuloendothelial system. Furthermore, we reported that there was no significant difference between the cumulative concentrations of Indium-111 (111In) and 90Y-labeled anti-CD20 mAb in plasma, which helped to validate the use of 111In as a surrogate for 90Y-anti-CD20 mAb for use in biodistribution and dosimetry studies. On the basis of this and other data, the preinfusion of unlabeled anti-CD20 mAb was used in subsequent studies of this radiolabeled antibody.

In this article, we also reported that nonhematologic toxicity was minimal and that doses up to 40 mCi of 90Y-anti-CD20 were not myelosuppressive. The overall response rate was 72% in 18 patients with relapsed low- or intermediate-grade non-Hodgkin lymphoma. There were six complete responses (CR) and seven partial responses (PR), with freedom from progression (FFP) of 3 to 19+ months. In addition, retreatment at the 40-mCi dose level resulted in two PRs and was well tolerated. These results were very promising for this patient population, many of whom were chemotherapy refractory, demonstrating the potential of this therapy to result in durable responses with a toxicity profile that compared very favorably with that of chemotherapy. Importantly, these findings provided a compelling rationale for further study of this therapy, including a pivotal study that supported FDA approval of this antibody, then known as 90Y-ibritumomab tiuxetan (Zevalin; Spectrum Pharmaceuticals, Inc.), which uses the chimeric anti-CD20 antibody, rituximab, for predosing. In this study, 143 patients were randomized to receive rituximab alone as four weekly doses of 375 mg/m2 (as used as a therapeutic agent alone or in combination with chemotherapy) or radioimmunotherapy with 250 mg/m2 rituximab for predosing, which optimized the biodistribution of 111In-labeled ibritumomab tiuxetan for biodistribution studies, followed 7 days later by a preinfusion of 250 mg/m2 rituximab and then 0.4 mCi/kg Zevalin (dose reduced to 0.3 mCi/kg for platelet counts between 100,000–149,000) for therapy. In this study, the overall response rate of Zevalin was 80% (30% CRs) as compared with a 56% response rate for rituximab with 16% CRs, with time to next therapy for those patients who progressed of 11.5 months for Zevalin and 7.8 months for rituximab (3). This therapy was also efficacious in patients after the use of rituximab (4). The initial approval for Zevalin was for patients with relapsed or refractory low-grade or transformed B-cell non-Hodgkin lymphoma, including patients who experienced disease progression on rituximab. Zevalin was also subsequently approved for upfront treatment of previously untreated patients with low-grade B-cell lymphoma.

These results stimulated additional trials to study the efficacy and safety of this therapy as retreatment of patients who had previously benefited from this therapy, as salvage therapy for patients who had failed bone marrow transplantation, and in other histologies (e.g., diffuse large-cell lymphoma (DLCL), mantle cell lymphoma, and others). In an effort to further improve the therapeutic index of this treatment, Zevalin was integrated into combined modality approaches with either radiation therapy or chemotherapy. For example, in a randomized phase III study of chemotherapy followed by observation or Zevalin in 409 patients with advanced-stage follicular lymphoma, the projected tumor dose was reduced to 40.3 cGy/mCi. The improved biodistribution of the radiolabeled antibody following administration of unlabeled antibody was presumably due, at least in part, to decreased nonspecific uptake of antibody by cells with Fc receptors in the reticuloendothelial system. Furthermore, we reported that there was no significant difference between the cumulative concentrations of Indium-111 (111In) and 90Y-labeled anti-CD20 mAb in plasma, which helped to validate the use of 111In as a surrogate for 90Y-anti-CD20 mAb for use in biodistribution and dosimetry studies. On the basis of this and other data, the preinfusion of unlabeled anti-CD20 mAb was used in subsequent studies of this radiolabeled antibody.

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lymphoma, at a median follow-up of 7.3 years, Zevalin consolidation in patients with a PR or better resulted in a 3-year benefit in median progression-free survival (PFS), with a durable 19% advantage at 8 years, and improved median time to next treatment of 5.1 years (3). Other studies have evaluated the potential role of Zevalin as consolidative therapy following chemotherapy with or without rituximab in patients with previously untreated stage I and II DLCL, in which 88% of patients treated with rituximab; cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy; and Zevalin had ongoing CRs, and 98% were alive at 4 years (6). These and other studies have demonstrated a significant benefit of consolidative radioimmunotherapy in terms of CR rate and duration of response (7). Importantly, radioimmunotherapy in this patient population does not preclude subsequent treatment with chemotherapy or stem cell transplantation, with toxicity from these additional treatments being similar to that in patients not previously treated with radioimmunotherapy.

In an effort to further improve on the results from these trials, preclinical studies were conducted to develop improved chelators, explore the use of a variety of other radionuclides, and combine radioimmunotherapy with biologic response modifiers (e.g., bortezomib) and immunostimulatory agents (e.g., CpG). Pretargeting approaches using an anti-CD20 fusion peptide were also developed. This platform technology dissociated the delivery of antibody from the delivery of radionuclide, with a clearing agent used in between to eliminate unbound circulating antibody, that, if radiolabeled, results in nonspecific radiation and associated toxicity. Promising results using this approach were obtained in a clinical trial (8), in which significantly increased tumor:whole body, tumor:blood, and tumor:normal organ ratios were obtained compared with that achievable with directly labeled mAb. Other pretargeting approaches have explored the use of bifunctional antibodies. The use of innovative carriers, such as engineered antibody fragments and constructs, has also been studied preclinically.

Overall, the use of $^{90}$Y-anti-CD20 mAb provided a novel targeted therapy for the treatment of recurrent and refractory B-cell lymphoma, with impressive efficacy and very acceptable toxicity. It provided a new therapeutic paradigm for this and other diseases. The success of this therapy was based on the preclinical and clinical work of many investigators in the field. Early clinical trials were based on promising in vitro and in vivo preclinical models. The encouraging results from the early clinical trials raised additional questions best addressed in the laboratory in an effort to further improve on the efficacy of this therapy. Results from this subsequent work contributed to such advances as pretargeted therapies and the use of alternative radionuclides, with potentially more beneficial emission profiles, including alpha emitters currently in use for the treatment of leukemia. Altogether, this work and that of numerous others lay the groundwork for the development of many targeted therapies under development and available today. Lessons to be learned from the development of radioimmunotherapy for the treatment of B-cell lymphoma come from the observation that despite impressive clinical results (better than with many current agents under investigation), radioimmunotherapy has not been broadly adopted, nor been a particular market success. This demonstrates the need to be cognizant of current practice patterns, as well as logistical and financial aspects of new therapies—a lesson that is relevant to the development of many personalized medicine therapies in the pipeline.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Authors’ Contributions**

Conception and design: S.J. Knox, R. Levy
Writing, review, and/or revision of the manuscript: S.J. Knox, R. Levy

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**References**

CCR 20th Anniversary Commentary: Radioactive Drones for B-cell Lymphoma

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