

## Radioimmunotherapy in non-Hodgkin's lymphoma: can it change the course of the disease?



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A B S T R A C T

Despite the advent of numerous new chemotherapeutic agents over the last 25 years, only limited progress in the treatment of non-Hodgkin's lymphoma (NHL) has been made with these agents alone. In recent years, several new antibody-based treatments have demonstrated promising results in NHL suggesting tangible improvements in relapse free and overall survival. These new treatment approaches have included radioimmunotherapy (RIT) with  $^{90}\text{Y}$ -labeled ibritumomab tiuxetan and  $^{131}\text{I}$ -labeled tositumomab. RIT utilizes continuous delivery of low-dose radiation via radioactive isotopes conjugated to monoclonal antibodies that target the CD20 antigen located on most (>90%) B-cell lymphomas. Clinical trials of  $^{90}\text{Y}$ -ibritumomab tiuxetan and  $^{131}\text{I}$ -tositumomab have indicated that these agents are effective and well tolerated for adult patients with relapsed or refractory CD20<sup>+</sup> follicular B-cell NHL, with the ability to produce superior overall and complete response rates to those achieved with existing therapies. A high proportion of patients who achieve a complete response with  $^{90}\text{Y}$ -ibritumomab tiuxetan or  $^{131}\text{I}$ -tositumomab exhibit durable remissions of several years - despite the presence of risk factors for poor response or early relapse. In addition, failure to respond to previous anti-lymphoma therapy, including rituximab, does not appear to preclude achieving a long-term response with  $^{90}\text{Y}$ -ibritumomab tiuxetan. RIT with  $^{90}\text{Y}$ -ibritumomab tiuxetan or  $^{131}\text{I}$ -tositumomab has also been shown to be effective in patients with follicular NHL when used as first-line therapy or following first-line, short-course chemotherapy  $\pm$  rituximab regimens, but further clinical studies are needed to determine the long-term efficacy of these approaches.

### Introduction

The prolongation of survival in patients with non-Hodgkin's lymphoma (NHL) has posed a considerable clinical challenge. In patients with the follicular lymphoma, which accounts for approximately 22% of all NHL cases, the prognosis and treatment are related to the extent of the disease at initial diagnosis.<sup>1,2</sup>

Follicular lymphoma (FL) has been known to be

very radiosensitive for well over 50 years, and durable remissions after radiotherapy are achievable in patients with both early- and late-stage disease.<sup>3</sup> Patients with recurrent disease have also shown promising response to radiotherapy, with some studies reporting overall response rates after the first round of treatment of 92%. Importantly, the response rate in these patients was found not to be related to history of previous regimens, FL grade and number of positive sites, or the largest

lymphoma diameter.<sup>3</sup>

In the majority of cases, NHL is detected at an advanced stage and is generally incurable with conventional therapeutic approaches, such as chemotherapy or radiotherapy. Despite the advent of numerous chemotherapeutic agents in recent years, only limited progress in the treatment of FL has been made with chemotherapy alone. Until recently, combination chemotherapy regimens have had no major impact on survival, which has remained largely unchanged for more than four decades, with median survival times of 8 to 10 years.<sup>2,4,5</sup> While remission can be achieved in many patients (60–80%), the majority are not cured, which suggests that the major obstacle to achieving a cure is the continuing survival of resistant neoplastic cells.

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### Emergence of immunotherapy

In recent years, several new treatments have demonstrated promising results in NHL. Immunotherapy with the monoclonal antibody rituximab, initially alone and later in combination with radioimmunotherapy (RIT) has been a major therapeutic advance in the last few years. Both treatments target the CD20 antigen.<sup>6</sup> The CD20 antigen (B-lymphocyte-restricted differentiation antigen; Bp35) is a hydrophobic transmembrane protein expressed on both normal and malignant B-cells and has a role in regulating B-cell activation.<sup>7,8</sup> However, it is not found on precursors to B-cells, normal plasma cells, or other normal tissues, and is not shed from the cell surface or internalized after anti-CD20 antibody binding.<sup>9,10</sup>

Rituximab, an unconjugated, chimeric/human monoclonal antibody is indicated for the treatment of patients with relapsed or refractory low-grade or follicular CD20<sup>+</sup> B-cell NHL. However, only approximately 50% of

patients respond to rituximab monotherapy,<sup>11</sup> and additional treatment options are needed to improve response rates.

RIT utilizes radionuclides conjugated to monoclonal antibodies to take advantage of the ability of the monoclonal antibody to target the CD20 antigen located on most (>90%) B-cell lymphomas along with the high radiosensitivity of lymphoma cells.<sup>2,7</sup> In this regard, the use of RIT with radiolabeled anti-CD20 monoclonal antibodies offers several potential benefits since continuous delivery of low-dose radiation can induce radiolysis in both targeted and adjacent lymphoma cells via a radiation *cross-fire* effect.<sup>2</sup> This targeted radiation has led to improved response rates in comparison with rituximab in follicular and transformed NHL. A randomised study in patients with relapsed or refractory low-grade, follicular, or transformed CD20<sup>+</sup> NHL confirmed that <sup>90</sup>Y-ibritumomab tiuxetan produced clinically significant higher overall response rates ( $p=0.002$ ) and complete responses ( $p=0.04$ ) compared with rituximab alone.<sup>12</sup>

In the European Union, yttrium-90 (<sup>90</sup>Y)-ibritumomab tiuxetan is licensed for the treatment of patients with relapsed or refractory follicular B-cell NHL, while in the US, <sup>90</sup>Y-ibritumomab tiuxetan and iodine-31 (<sup>131</sup>I)-labeled tositumomab are currently approved for use in patients with relapsed FL in the US. <sup>90</sup>Y-ibritumomab tiuxetan consists of a murine anti-CD20 monoclonal antibody (ibritumomab) covalently attached to a metal chelator molecule tiuxetan and the radioisotope <sup>90</sup>Y. <sup>90</sup>Y has a number of advantages over <sup>131</sup>I, including delivery of radiolysis energy five-times greater than <sup>131</sup>I, a longer path length of effective radiation, a shorter half-life (~64 hours), and less radiation exposure to non-target organs and to medical personnel and patient caregivers. Whereas <sup>131</sup>I emits both  $\beta$  and  $\gamma$  radiation, <sup>90</sup>Y is a pure  $\beta$ -emitter and <sup>90</sup>Y-ibritumomab tiuxetan can be administered in

an outpatient setting, and there is no need to determine activity limits or dose rate limits.

<sup>131</sup>I-tositumomab is a murine IgG2a antibody radiolabeled with Iodine-131. Iodine-131 has a long history of clinical use associated with rapid renal clearance and a lack of accumulation in bone.<sup>13</sup> Iodine-131 produces both  $\beta$  and  $\gamma$  radiation. <sup>131</sup>I-tositumomab is delivered using patient-specific dosimetry to deliver 65cGy-75cGy as a whole body dose.

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### <sup>90</sup>Y-ibritumomab tiuxetan clinical trial experience

The initial clinical development of <sup>90</sup>Y-ibritumomab tiuxetan comprised three early phase (I/II) clinical trials and two phase III studies in patients with relapsed or refractory low-grade NHL; these studies utilized standardized US National Cancer Institute (NCI) and International Workshop Response Criteria (IWRC) developed in collaboration with the US Food and Drug Administration (FDA) (Table 1). These clinical studies of <sup>90</sup>Y-ibritumomab tiuxetan all involved pretreatment with rituximab in order to improve tumor targeting with the radiolabeled monoclonal antibody.

A phase I/II open-label dose escalation study to determine the maximum tolerated dose (MTD) of <sup>90</sup>Y-ibritumomab tiuxetan that could be administered (without stem cell support) to patients with relapsed or refractory B-cell NHL indicated that this was 14.8 MBq (0.4 mCi)/kg or, in patients with baseline platelet counts of 100,000–149,000/ $\mu$ L, 11.1 MBq (0.3 mCi)/kg.<sup>14</sup> The overall response rate (ORR) for the intent-to-treat population of this study (n=51) was 67% (Table 1).

In a phase III, randomized, controlled comparative trial in 143 patients with relapsed or refractory, low-grade, follicular, or transformed B-cell NHL, a single intravenous (IV) dose of <sup>90</sup>Y-ibritumomab tiuxetan [15 MBq

(0.4 mCi)/kg] was found to be superior to a standard four-dose regimen of rituximab (375 mg/m<sup>2</sup> weekly) with regard to both the ORR (80% vs 56%;  $p=0.002$ ) and the complete response (CR) rate (34% vs 20%;  $p=0.063$ ) (Table 1).<sup>12</sup> In a subset of 113 patients with follicular, low-grade NHL, the ORR was 86% in the <sup>90</sup>Y-ibritumomab tiuxetan group versus 55% in the rituximab group ( $p<0.001$ ). After patients were stratified according to prognostic variables, <sup>90</sup>Y-ibritumomab tiuxetan still produced a superior response compared with rituximab. The ORR with <sup>90</sup>Y-ibritumomab tiuxetan was significantly higher than with rituximab in patients who were resistant to any prior chemotherapy (63% vs. 43%;  $p=0.078$ ), patients resistant to the last course of therapy (64% vs. 36%;  $p=0.045$ ), and patients with FL (76% vs. 47%;  $p<0.001$ ). Although the study was not powered to demonstrate differences in time-to-event variables, the results demonstrated a trend toward a longer time to progression (TTP), duration of response (DR), and time to next treatment (TTNT) in patients treated with <sup>90</sup>Y-ibritumomab tiuxetan compared with those treated with rituximab, particularly in patients with follicular NHL.<sup>12</sup>

Another phase III study in 57 patients with rituximab-refractory follicular NHL showed that a single IV dose of 15 MBq (0.4 mCi)/kg <sup>90</sup>Y-ibritumomab tiuxetan (preceded by two doses of 250 mg/m<sup>2</sup> rituximab to deplete peripheral blood B-cells) produced an ORR of 74% (CR 15%; PR 59%) and a median TTP of 6.8 months (8.7 months in responders) (Table 1).<sup>17</sup>

Based on the experience from these clinical trials, the currently recommended <sup>90</sup>Y-ibritumomab tiuxetan treatment regimen consists of two IV doses of rituximab 250 mg/m<sup>2</sup> on days 1 and 8 followed immediately by an IV *slow push* 10-minute infusion of <sup>90</sup>Y-ibritumomab tiuxetan 14.8 MBq/kg (0.4 mCi/kg) up to a maximum dose of 1200 MBq (32 mCi). Treatment can be given on an outpatient basis

Table 1: Efficacy of <sup>90</sup>Y-ibritumomab tiuxetan in patients with relapsed or refractory NHL according to International Workshop Response Criteria (IWRC).

Clinical trial	Description/ indication	No. of patients	<sup>90</sup> Y ibritumomab tiuxetan dose range	Response				
				ORR (%)	CR/CRu (%)	PR (%)	Median DR (months)	Median TTP (months)
Phase I uncontrolled, open-label <sup>10</sup>	Dose escalation Low- or intermediate-grade B-cell NHL	14	740–1850 MBq (20-50 mCi) 2220-2590 MBq (60–70 mCi) [n=3]	64 <sup>a</sup>	28 <sup>a</sup>	36 <sup>a</sup>	–	9.3
Phase I/II uncontrolled, open-label <sup>14,15</sup>	Dose escalation Low- or intermediate-grade B-cell lymphoma, mantle-cell NHL	51	7-15 MBq (0.2-0.4 mCi) /kg BW	67 <sup>a</sup> 73 <sup>b</sup>	26 <sup>a</sup> 51 <sup>b</sup>	41 <sup>a</sup> 22 <sup>b</sup>	11.7+ 11.7 <sup>b</sup>	12.9+ 9.3 <sup>b</sup>
Phase II uncontrolled, open-label <sup>16</sup>	Single arm Low-grade, CD20+ follicular, or transformed B-cell NHL, mild thrombocytopenia	30	11 MBq (0.3 3 mCi)/kg BW	44 8	40	11.5	13.9 <sup>c</sup>	
Phase III controlled, randomized, multicenter <sup>12</sup>	Two arm ( <sup>90</sup> Y ibritumomab tiuxetan vs rituximab) Low-grade, CD20+ follicular or transformed B-cell NHL	143	15 MBq (0.4 mCi)/kg BW vs Rituximab	80 56	34 20	45 36	14.2 12.1	11.2 10.1
Phase III open-label, non-randomized, multicenter <sup>17</sup>	Rituximab-refractory follicular and non-follicular (n=3) NHL	57	15 MBq (0.4 mCi)/kg BW	74	15	59	6.4 (8.7 <sup>d</sup> )	6.8

<sup>a</sup> Protocol-defined response criteria; <sup>b</sup> Long-term follow-up data<sup>15</sup>; <sup>c</sup> At 23.3 month follow-up. <sup>d</sup> In responders. BW, body weight; CR, complete response; CRu, complete response, unconfirmed; DR, duration of response; MBq, megabecquerel; mCi, millicurie; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; PR, partial response; TTP, time to progression.

and the dosage is calculated according to patient weight (up to a maximum of 1,184 MBq), with no requirement for dosimetry.

A further analysis of the integrated data from the four pivotal clinical trials in patients with relapsed or refractory B-cell NHL (n=211) compared the efficacy and safety of <sup>90</sup>Y-ibritumomab tiuxetan in patients who had received only one prior therapy (i.e. as second-line therapy) with those who had received 2 prior therapies (third-line plus therapy).<sup>18</sup> Patient characteristics were similar in the two groups, except that the second-line treatment group had a higher rate of lymphomatous marrow involvement, and there was a trend towards bulkier disease in the third-line plus treatment group. The benefits of earlier treatment with <sup>90</sup>Y-ibritumomab tiuxetan were notable, as the second-line therapy group had a higher ORR (86% vs.

72%;  $p=0.051$ ) and CR/CRu rate (49% vs. 28%;  $p=0.004$ ) than the third-line therapy group, and a longer median TTP (12.6 vs. 7.9 months;  $p=0.0038$ ) and DR (13.7 vs. 8.2 months;  $p=0.163$ ). Differences between the second- and third-line plus groups in the subset with follicular NHL (n=169) are shown in Figure 1; the CR/CRu rates in this subset were significantly higher in the second-line therapy group (54.7% vs 30.2%;  $p=0.004$ ). The incidence of grade 3/4 adverse events were similar between the two treatment groups.<sup>18</sup>

An additional analysis of data from these trials showed that the efficacy and safety of <sup>90</sup>Y-ibritumomab tiuxetan was maintained irrespective of age and prior treatment history.<sup>19</sup> In patients <60 years, 60-69 years and ≥70 years, 74–85% of whom had received 1–3 previous regimens, with 15–31% receiving ≥4 previous

regimens, there was no significant difference between age groups in ORR (71–80%;  $p=0.48$ ), CR/Cru rate (33–38%;  $p=0.89$ ), median DR (9.4–11 months;  $p=0.92$ ) or median TTP (8.4–8.8;  $p=0.77$ ). Grade 3/4 neutropenia was significantly less in the 60–69 year age group ( $p=0.03$ ), but there was no significant difference between age groups in the incidence of grade 3/4 thrombocytopenia or anemia.<sup>19</sup>

The potential therapeutic benefit of using RIT with <sup>90</sup>Y-ibritumomab tiuxetan as first-line treatment has also been investigated in studies in previously untreated patients with follicular NHL. Similarly, in a small series of 10 patients with previously untreated low-grade follicular NHL, first-line treatment with <sup>90</sup>Y-ibritumomab tiuxetan (preceded by two doses of rituximab) followed by rituximab maintenance therapy at 6-month intervals over 2 years produced a 100% response rate; 5 of 8 evaluable patients (62%) had a CR and 3 (38%) a PR.<sup>20</sup>

In addition, first-line, short-course chemotherapy plus rituximab (cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP]-R) followed by <sup>90</sup>Y-ibritumomab tiuxetan appeared highly active and well tolerated in a study of 42 patients with follicular NHL. Interestingly, the CR rate in these patients increased from 30% with chemotherapy/rituximab to 67% after <sup>90</sup>Y-ibritumomab tiuxetan treatment.<sup>21</sup>

### Durability of the response to <sup>90</sup>Y-ibritumomab tiuxetan

One of the most interesting and potentially important findings to emerge in the long-term follow-up of the patients enrolled in the phase I/II study is the excellent durability of response to treatment with <sup>90</sup>Y-ibritumomab tiuxetan.<sup>14</sup> After a median follow-up of 28.5 months (63 months for ongoing responders), the ORR increased to 73% (CR/Cru [unconfirmed CR]

51%; PR 22%) (Table 1).<sup>15</sup> In the subgroup with follicular NHL (n=33), the ORR was 85%, compared with 58% for those with diffuse large B-cell NHL (n=12). Among the 37 patients who responded to <sup>90</sup>Y-ibritumomab tiuxetan, the median TTP was 12.6 months (Figure 2), and 9 of these patients had a TTP of more than 3 years. In 5 cases, patients were still in remission at the time of follow-up and the DR was more than 5 years (60 to >74 months).<sup>15</sup>

Similarly, updated time-to-event data (median 44 months follow-up) for the phase III randomized, controlled study comparing <sup>90</sup>Y-ibritumomab tiuxetan with rituximab<sup>12</sup> indicated a continuing trend towards longer TTP (15.0 vs. 10.2 months;  $p=0.07$ ) and TTNT (21.1 vs. 13.8 months;  $p=0.27$ ) with <sup>90</sup>Y-ibritumomab tiuxetan compared with rituximab in the subgroup with follicular NHL (Figure 3).<sup>22</sup>

Overall, ongoing follow-up of patients treated in four registration trials of <sup>90</sup>Y-ibritumomab tiuxetan conducted at 30 US-based centres have indicated that durable long-term responses were achieved in 37% of all patients with relapsed or refractory B-cell NHL (n=211) and 39% of those with follicular NHL (n=153).<sup>23</sup> In

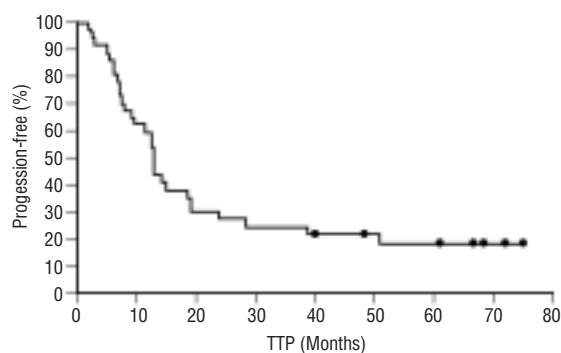


Figure 1: Kaplan-Meier analysis of time to progression (TTP) in 37 patients with relapsed or refractory B-cell NHL (mostly with follicular histology) who responded to <sup>90</sup>Y-ibritumomab tiuxetan (International Workshop Response Criteria; median TTP = 12.6 months).<sup>15</sup> Reproduced with permission from Gordon L, et al. Durable responses after ibritumomab tiuxetan radioimmunotherapy for CD20<sup>+</sup> B-cell lymphoma: a long-term follow-up of a phase 1/2 study. *Blood* 2004;103:4429-31.



those who met the criteria for long-term response (n=78), the median DR and TTP were 28.1 months and 29.3 months, respectively. Fifty-one of the 78 patients (65%) achieved complete responses (CR + CRu), and the median TTP in patients with an ongoing response was 53.9 months (Figure 4).<sup>24</sup> It was concluded that <sup>90</sup>Y-ibritumomab tiuxetan produced durable long-term responses in patients with relapsed or refractory B-cell NHL, including those at high risk for a poor response or early relapse. In addition, failure to respond to prior therapy did not appear to preclude achieving a long-term response with <sup>90</sup>Y-ibritumomab tiuxetan.<sup>24</sup>

#### <sup>131</sup>I-tositumomab clinical trial experience

<sup>131</sup>I-tositumomab treatment is initiated with a dosimetric step on day 0 at which time patients receive tositumomab 450 mg administered intravenously over 60 minutes, followed by <sup>131</sup>I-tositumomab (consisting of 5.0 mCi Iodine-131 and tositumomab 35 mg) administered intravenously over 20 minutes.<sup>25</sup> On days 7–14 patients receive therapeutic treatment with tositumomab 450 mg administered intravenously over 60 minutes, followed by <sup>131</sup>I-tositumomab (consisting of the prescribed therapeutic dose of Iodine-131 and tositumomab 35 mg) administered intravenously over 20 minutes.

Kaminski et al. reported highly impressive results with <sup>131</sup>I-tositumomab in 76 previously untreated patients with advanced FL with an ORR of 95%, a CR rate of 75% and an actuarial disease free survival of 59% at 5 years.<sup>26</sup>

<sup>131</sup>I-tositumomab has also been investigated as consolidation after chemotherapy. The sequential use of abbreviated fludarabine chemotherapy prior to <sup>131</sup>I-tositumomab was found to be highly effective as first-line therapy in 35 low- or intermediate-risk patients with follicular

NHL.<sup>27</sup> All 35 patients responded, with 30 (86%) achieving a CR and 5 (14%) a PR.

In another study, CVP chemotherapy followed by <sup>131</sup>I-tositumomab treatment in 30 previously untreated patients with stage II-IV FL resulted in a response rate of 100%.<sup>28</sup> After

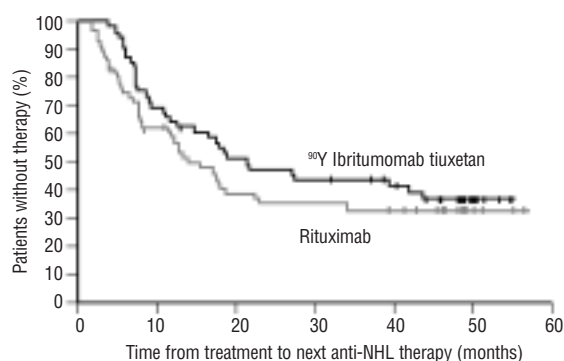


Figure 2: Time to next anti-NHL therapy in the subgroup of patients with follicular NHL who received either a single IV dose of <sup>90</sup>Y-ibritumomab tiuxetan (preceded by two doses of rituximab to improve biodistribution and one dose of <sup>111</sup>In-ibritumomab tiuxetan for imaging; n=55) or 4 weekly intravenous doses of rituximab (n=58).<sup>22</sup> Reprinted from Gordon L, et al. Yttrium 90-labeled ibritumomab tiuxetan radioimmunotherapy produces high response rates and durable remissions in patients with previously treated B-cell lymphoma. *Clin Lymphoma* 2004;5:98-101. ©2004, with permission from Cancer Information Group.

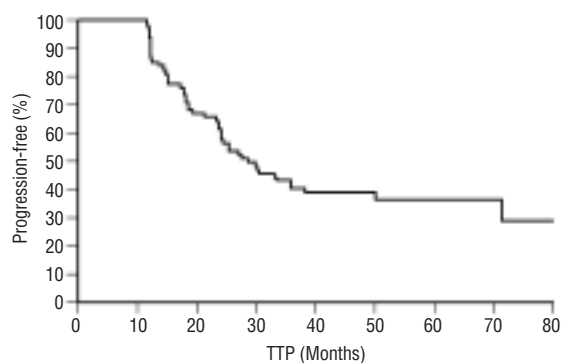


Figure 3: Kaplan-Meier estimates of the time to progression (TTP) in 78 patients with relapsed or refractory B-cell NHL (mostly with follicular histology) who met the criteria for a long-term response ( $\geq 12$  months) with <sup>90</sup>Y-ibritumomab tiuxetan.<sup>24</sup> Reproduced with permission from Wiseman GA, et al. Yttrium-90 (<sup>90</sup>Y) ibritumomab tiuxetan (Zevalin<sup>®</sup>) induces long-term durable responses in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. *Cancer Biother Radiopharm* 2005;20:185-8.

chemotherapy alone, the CR was 50%, while the PR was 50%; after <sup>131</sup>I-tositumomab treatment, 9 of 15 PR patients converted to a CR, resulting in an overall 80% CR. After 2.3 years follow-up, 77% of these patients remained in response, and median PFS was not yet reached.<sup>28</sup> Similarly, another group of 90 patients with stage II-IV FL had 90% remis-

sion rates after CHOP and <sup>131</sup>I-tositumomab treatment (54% CR/12%CRu).<sup>29</sup> The 2-year overall survival rate in this study was 97%.

The 4-year PFS for patients with advanced stage FL receiving first-line treatment with CHOP and a monoclonal antibody (MoAb) [rituximab or <sup>131</sup>I-tositumomab] was 61%, a significant ( $p=0.005$ ) improvement over conventional therapies. The 4-year overall survival was also significantly improved in patients treated with chemotherapy plus monoclonal antibody compared with CHOP and ProMACE regimens (91% vs 69 and 79%;  $p<0.001$ ).<sup>30</sup> These results demonstrate that the treatment of FL has been revolutionized by monoclonal antibody therapy.

The efficacy of <sup>131</sup>I-tositumomab was also assessed in 60 patients with low-grade or transformed low-grade B-cell NHL relapsing within 6 months of treatment with at least two prior chemotherapy regimens.<sup>13</sup> The ORR was 65% following treatment with <sup>131</sup>I-tositumomab, compared with an ORR of 28% after their previous chemotherapy regimen ( $p<0.001$ ). Just 3% of patients were able to achieve a CR with their previous chemotherapy, compared with 20% of patients with <sup>131</sup>I-tositumomab ( $p<0.001$ ). The median DR for CR was 6.1 months with their previous chemotherapy but was not reached after more than 47 months of follow-up following <sup>131</sup>I-tositumomab treatment.

An integrated efficacy analysis of 5 clinical trials of <sup>131</sup>I-tositumomab in 250 patients with relapsed or refractory low-grade or transformed NHL showed similar findings.<sup>31</sup> The ORR in the 5 trials ranged from 47% to 68% (mean 56%), and the CR ranged from 20% to 38% (mean 30%). The 5-year PFS was 17%, with 32% of patients having a PFS of  $\geq 1$  year.

Despite these promising results, further studies will be required to determine the long-term efficacy of these treatment approaches. Indeed, studies of radioimmunotherapy to treat NHL

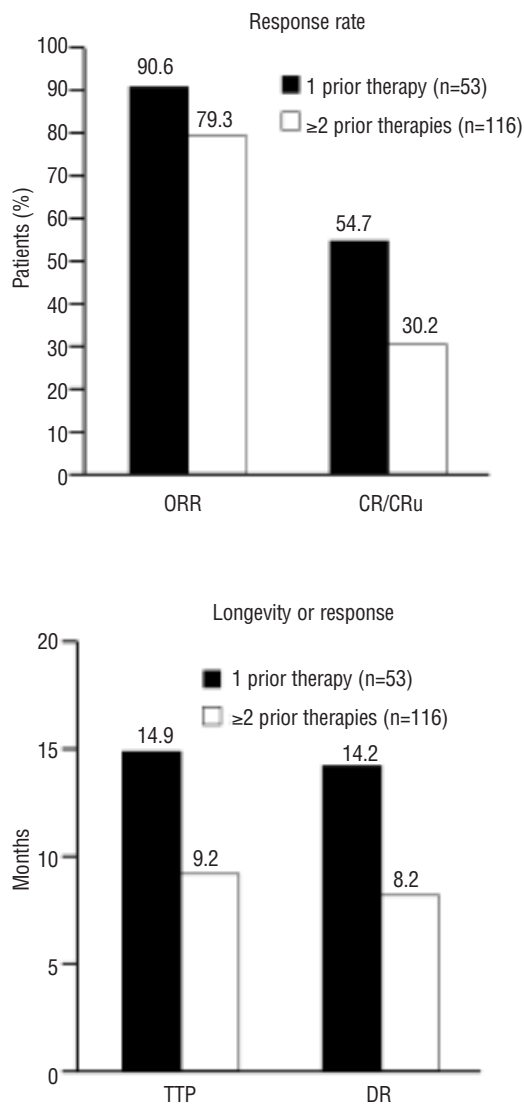


Figure 4: Efficacy of second-line or third-line plus <sup>90</sup>Y-ibritumomab tiuxetan treatment in 169 patients with previously treated follicular NHL (integrated analysis of 4 clinical trials).<sup>18</sup> CR, complete response; CRu, complete response, unconfirmed; DR, duration of response; ORR, overall response rate; TTP, time to progression.

are still ongoing; a large (n=400), randomized, open label international study of the efficacy and safety of <sup>131</sup>I-tositumomab treatment in patients in complete remission after first-line CHOP-R therapy is underway and results from this study are awaited with interest.

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## Conclusions

RIT with <sup>90</sup>Y-ibritumomab tiuxetan or <sup>131</sup>I-tositumomab represents an attractive treatment option for patients with relapsed or refractory follicular B-cell NHL, with the ability to produce superior response rates to those achieved with existing therapies. RIT with <sup>90</sup>Y-ibritumomab tiuxetan and <sup>131</sup>I-tositumomab allows many patients to experience durable remissions for a number of years, and evidence is emerging to suggest that such treatments may be able to change the course of FL. Studies in patients with follicular NHL have also indicated the potential benefits of RIT as first-line therapy and following first-line, short-course chemotherapy + rituximab regimens, but further clinical studies are needed to determine the long-term efficacy of these approaches, and the role RIT could play in the future treatment of other NHL.

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