

**REGIONAL DRUG AND THERAPEUTICS CENTRE
(NEWCASTLE)**

**THE USE OF IBRITUMOMAB IN THE
MANAGEMENT OF B-CELL FOLLICULAR
NON-HODGKIN'S LYMPHOMA**

**Wolfson Unit
Claremont Place
Newcastle upon Tyne
NE2 4HH**

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ABOUT THIS REPORT

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre. The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rests solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

Subject	Date issued
Alglucerase for Gaucher's disease	July 1997
Taxanes in breast cancer	July 1997
Somatropin for GHD in adults	January 1998
New drugs for Alzheimer's disease	February 1998
Atypical antipsychotics	February 1998
Dornase alfa for cystic fibrosis	July 1998
Topotecan for ovarian cancer	July 1998
Irinotecan for colorectal cancer	July 1998
Interferon alfa for haematological malignancy	July 1998
Antiretroviral therapy	July 1998
Paclitaxel in ovarian cancer	December 1998 (update)
Interferon in MS	May 1999 (update)
Octreotide	July 1999
Drug treatment of obesity	July 1999
Low molecular weight heparins in venous thrombo-embolic disease	November 1999
Low molecular weight heparins in unstable coronary artery disease	November 1999
Ribavirin and interferon alfa for chronic hepatitis C	March 2000
Temozolomide for high grade gliomas	May 2000
New drugs for rheumatoid arthritis	May 2000
Verteporfin for age related macular degeneration	November 2000
Iloprost and epoprostenol in the management of pulmonary hypertension	February 2001
Atypical antipsychotics in the management of dementia	June 2001
Interferon alfa in the management of malignant melanoma	November 2001
Imatinib (Glivec [®] , STI-571), in the management of chronic myeloid leukaemia	November 2001
Agalsidase alfa and beta in the management of Fabry disease	July 2002
Carbamyl glutamate in the management of N-acetylglutamate synthetase deficiency	July 2002
Erythropoietin in the management of cancer related anaemia	July 2002
Drotrecogin alfa (activated) in the management of severe sepsis	December 2002
An update on newer agents for the treatment of pulmonary hypertension	February 2004
The use of adefovir dipivoxil for the treatment of chronic hepatitis B infection	May 2004
The use of teriparatide in the management of osteoporosis	July 2004
The use of ibandronic acid in the management of hypercalcaemia of malignancy, bone pain and the prevention of skeletal events associated with skeletal metastases	August 2005
The use of pegvisomant in the management of acromegaly	January 2006
The use of pemetrexed in the management of malignant pleural mesothelioma	February 2006
The use of bortezomib second-line in the management of multiple myeloma	March 2006
The adjuvant use of docetaxel or paclitaxel in the management of early stage breast cancer	March 2006
The use of erlotinib in the management of non-small cell lung cancer	March 2006
The use of rituximab in combination with CVP chemotherapy for the management of follicular non-Hodgkin's lymphoma	March 2006

SUMMARY

- The annual incidence in the UK of follicular lymphomas is between 3 – 5 per 100,000 and prevalence is about 40 per 100,000. Most follicular lymphomas present at stages III or IV.
- Therapeutic options are limited in the treatment of relapsed or refractory, low-grade, follicular, or transformed non-Hodgkin's lymphoma. Almost all patients relapse, regardless of the regimen used, and no single therapy shows definitive value in increasing survival for this patient population.
- Ibritumomab is a monoclonal antibody attached to a radioisotope (Yttrium⁹⁰) by a linking agent (tiuxetan). It is designed to deliver radiation to lymphoma cells. It targets the CD20 antigen, which is unique to B-lymphocytes. Ibritumomab is licensed for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma.
- Ibritumomab has been evaluated in one phase III, two phase II and one phase I/II trial. In pre-treated, rituximab refractory patients, overall response rate was 74% with median time to progression of 6.8 months and a duration of response of 6.4 months. When ibritumomab was compared to rituximab in follicular non-Hodgkin's lymphoma patients, overall response rates were 86% and 55% respectively.
- The most common non-haematological side effects reported are gastrointestinal including nausea, vomiting and anorexia, and respiratory, mainly cough, infection and bronchospasm. Haematological toxicity includes neutropenia, thrombocytopenia and anaemia, caused by the effect of radiation on the stem cells. Severe, prolonged neutropenia has been associated with an increase in complicating infections.
- According to the manufacturers, the total cost is £10,356 per patient per treatment (exclusive of VAT), including rituximab costs. Assuming that a third of follicular non-Hodgkin's lymphoma patients do not respond to rituximab and are potentially suitable for treatment with ibritumomab (1 – 2 per 100,000), this corresponds to a potential total annual cost of between £10,356 and £20,712 per 100,000 population.
- Ibritumomab should only be handled and administered by personnel authorised to use and manipulate radionuclides in a designated clinical setting. There is limited trial evidence to suggest that ibritumomab could be considered in follicular non-Hodgkin's lymphoma patients who are rituximab relapsed or refractory.

BACKGROUND

Non-Hodgkin's lymphomas, of which follicular lymphomas are a subgroup, are a heterogeneous group of tumours that affect the lymphatic system. Patients who develop the most common type of follicular lymphoma typically survive for a median of 8 to 10 years. The disease is incurable at advanced stages [stages III or IV, (Appendix 1)], and is curable in only about 5% of patients in earlier stages. Most follicular lymphomas present at stages III or IV.¹

Non-Hodgkin's lymphoma accounts for about 2% of all malignancies in the UK and there are about 9,000 new cases each year. The annual incidence for men is 15 per 100,000 population and for women it is 10 per 100,000. Between 22% and 40% of non-Hodgkin's lymphomas are follicular, depending on the classification. The annual incidence of follicular lymphomas is between 3 – 5 per 100,000 and prevalence is about 40 per 100,000.¹

The main aims of treatment are to achieve remission during relapse and to alleviate symptoms. Treatment is usually started with single agents such as an oral alkylating agent or combination CVP (cyclophosphamide, vincristine and prednisolone). When first-line treatment fails or relapse occurs, combination chemotherapy is given e.g. CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) or CVP. Both combination therapy and radiation therapy (appropriate only in a small proportion of patients) can produce prolonged remissions.¹ Therapeutic options are limited in the treatment of relapsed or refractory, low-grade, follicular, or transformed non-Hodgkin's lymphoma. Almost all patients relapse, regardless of the regimen used, and no single therapy shows definitive value in increasing survival for this patient population.²

Ibritumomab (Zevalin[®], Schering Ltd) is a monoclonal antibody attached to a radioisotope (⁹⁰Yttrium) by a linking agent (tiuxetan). It is designed to deliver radiation to lymphoma cells. It targets the CD20 antigen, which is unique to B lymphocytes.³

Ibritumomab is the murine, parent anti-CD20 antibody that was engineered in the development of rituximab. Tiuxetan is a linker/chelator covalently attached to ibritumomab. Ibritumomab tiuxetan can chelate ⁹⁰Y for therapy. Thus, the antibody specifically targets radiation to CD20+ cells while sparing normal nonlymphoid cells.⁴

Patients are pre-treated with an infusion of unlabelled rituximab 7 days before ibritumomab treatment. This is thought to remove normal cells carrying the CD20 antigen from the peripheral blood system. This prevents radioactivity being distributed throughout the body by circulating lymphocytes. On the eighth day, ibritumomab is given as a slow intravenous infusion, following a second infusion of rituximab.³

Ibritumomab is licensed for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma. Dosages are:

- For patients with 150,000 platelets per mm³ and more: 15 MBq/kg [⁹⁰Y] – radiolabelled ibritumomab up to a maximum of 1200 MBq.
- For patients with less than 150,000 but more than 100,000 platelets per mm³: 11 MBq/kg [⁹⁰Y]-radiolabelled ibritumomab up to a maximum of 1200 MBq.⁵

CURRENT GUIDANCE

The Scottish Medicines Consortium reviewed ibritumomab in April 2005, and concluded;⁶

“Ibritumomab is not recommended for use within NHS Scotland for the preparation of a radiopharmaceutical incorporating Yttrium 90 for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma.”

They did state however, that “No economic information was submitted to allow an assessment of its cost effectiveness” and this may have affected their decision.

NICE examined the use of rituximab for recurrent or refractory stage III or IV follicular non-Hodgkin's lymphoma in March 2002, and concluded that;¹

- The use of rituximab for third line or subsequent line, but not ‘last line’ treatment of patients with recurrent or refractory stage III or IV follicular lymphoma is not recommended
- For last line treatment, rituximab is recommended only in the context of a prospective case series. All patients for whom alternative therapies have been exhausted (those who are either chemo resistant or chemo intolerant) would be appropriate for inclusion in the case series on the basis that data are systematically collected to allow aggregation and analysis at a national level.¹

A Single Technology Appraisal is planned by NICE on rituximab as first line treatment for low grade non Hodgkin's lymphoma. This is expected to be published in August 2006.⁷

EFFICACY

Ibritumomab has been evaluated in one phase III, two phase II, one phase I/II trial and a safety study. Some of these studies have additional follow up data.

One phase II trial⁴, examined ibritumomab in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. This had been an extensively pre treated population (prior treatment with rituximab). The aim of this study was to evaluate whether rituximab refractory patients could achieve responses with an anti CD20 radioimmunotherapy (ibritumomab) directed against the same epitope as rituximab.

The primary end point was a target overall response rate of at least 35%. Secondary endpoints included time to progression and duration of response.

Eligible patients had undergone prior treatment with rituximab, and either did not respond or had a time to progression of less than 6 months. 90% patients were stage III/IV at study entry. 57 patients were enrolled and 54 had follicular non-Hodgkin's lymphoma. In these follicular patients, overall response rate was 74% (15% complete response and 59% partial response). Median time to progression was 6.8 months (1.1 to \geq 25.9 months) and for the 40 responders, median time to progression was 8.7 months (1.7 to \geq 25.9 months). Median duration of response was 6.4 months (0.5 to \geq 24.9 months).

The phase III, randomised, controlled trial was published in 2002,² comparing the overall response rate of patients who received ⁹⁰Y ibritumomab with those who received rituximab. Patients had advanced disease, relapsed or refractory low-grade or follicular or transformed non-Hodgkin's lymphoma with a median of two prior regimens. Primary endpoint was the overall response rate. Secondary endpoints included time to progression and duration of response.

143 patients were enrolled, and the overall response rate was 80% in the ibritumomab group, and 56% in the rituximab group (p=0.002). Estimated median time to progression was 11.2 months and 10.1 months respectively (p=0.173) and estimated median duration of response was 14.2 and 12.1 months respectively (p=0.644).

Of the 143 patients enrolled, 113 had follicular, low grade non-Hodgkin's lymphoma. In this subgroup, the overall response rate was 86% in the ibritumomab group and 55% in the rituximab group (P<0.001). The estimated median time to progression in this subgroup was 12.6 months and 10.2 months respectively (P=0.062). The estimated median duration of response was 18.5 months and 12.1 months respectively (p=0.371). Although the overall response rate was significantly higher in the ibritumomab group, compared with the rituximab group, this did not translate into a statistically longer time to progression, though the trial was not powered to detect differences in time to progression.

Patients in this trial were followed up for a further two years, and the data was published in 2004. The results of median times to event were;⁸

	Ibritumomab		Rituximab		p value
	No. of patients	Median (Months)	No. of patients	Median (Months)	
Time to progression for all patients	55	15.0	58	10.2	0.07
Time to progression for responders	47	17.8	32	13.2	0.55
Time to next anticancer treatment	55	21.1	58	13.8	0.27

A further phase I/II dose escalation study⁹ included 51 patients who had histologically confirmed, relapsed or refractory low grade or follicular B-cell non-Hodgkin's lymphoma who had failed two prior regimens or one anthracycline containing regimen. Patients were treated with varying strengths of ibritumomab (0.2 – 0.4 mCi/kg, equivalent to 7.4 - 14.8 MBq/kg). Overall response rate in all patients was 73% and in follicular patients (n=33), 85%. Median time to progression in all patients was 9.3 months, and in responders (n=37), 12.6 months, but it is not known what percentage of these were follicular patients. This trial provided longer term follow up data showing a median duration of response of 11.7 months in all patients (range 0.7 – 74.3 months). Seven years after commencing the study, 5 patients remained in remission, showing some evidence of durable responses.

A final, small phase II, multicentre trial¹⁰ evaluated reduced doses of ibritumomab in 30 patients with mild thrombocytopenia and relapsed or refractory low-grade non-Hodgkin's lymphoma. Thrombocytopenia is an additional clinical problem encountered when treating this disease. 83% patients had follicular lymphoma.

The overall response rate in all patients was 83% (37% complete response, 6.7% complete response unconfirmed and 40% partial response) and in follicular patients was 92%. The estimated median time to progression in all patients was 9.4 months (1.7 - 24.6 months), and in follicular patients was 10.8 months. Estimated median duration of response was 11.7 months (3.6 - 23.4 months). Patients were followed up for a median of 36.5 months, and this follow up study was published.¹¹ The median duration of response in this follow up study was 11.5 months (1.0 - 53.9 months) and median time to progression was 9.4 months (1.7 - 54.8 months). 7 patients have now died – 6 due to disease progression and 1 due to other causes.

It was concluded that patients with mild thrombocytopenia could safely and effectively receive reduced doses of ibritumomab, (although patient numbers in this trial were small).

ADVERSE EFFECTS

A safety study has been published¹² evaluating a summary of safety data from 349 patients in a total of five studies. Patients were observed for up to four years after therapy or until their disease progressed. Patients with relapsed, refractory or transformed CD20+ B cell non-Hodgkin's lymphoma were included.

After the 0.4-mCi dose (equivalent to 14.8 MBq), the incidences of grade 4 neutropenia, thrombocytopenia and anaemia were 30%, 10% and 3% respectively. 7% patients were hospitalised with infection and 4% had grade 3 or 4 events. Grade 1 or 2 neutropenia occurred in 40% patients and grade 1 or 2 thrombocytopenia occurred in 37% patients. Infection or febrile neutropenia was reported in 29% patients, 5% experienced grade 3 or 4 events. The most common infections were non specific upper respiratory tract infections (7%) and urinary tract infections (5%). The primary toxicity was reversible myelosuppression.

Non-haematological adverse effects were reported for 80% of patients. The majority were grades 1 or 2. More serious grade 3 and 4 adverse effects were reported in 11%, with asthenia in 2% and abdominal pain in 1%. A summary is provided in the table below:

Incidence of adverse effects and haematologic toxicity¹²

Adverse Event	No of patients (%)
Neutropenia Grade 3	103 (30%)
Neutropenia Grade 4	105 (30%)
Thrombocytopenia Grade 3	185 (53%)
Thrombocytopenia Grade 4	35 (10%)
Anaemia Grade 3	46 (13%)
Anaemia Grade 4	14 (4%)
Asthenia	123 (35%)
Nausea	86 (25%)
Chills	73 (21%)
Fever	46 (13%)

20% patients had died by the conclusion of the study (70 of the 349 patients). 58 deaths were secondary to non-Hodgkin's lymphoma (n=56) or subsequent to chemotherapy induced toxicity (n=2). Five deaths were due to unrelated concurrent or pre-existing illness, 5 patients died of myelodysplasia/acute myelogenous leukaemia and 2 had an intracranial haemorrhage from head trauma while they were thrombocytopenic. (One of these patients was also taking warfarin and ibuprofen).

The EMEA states that the most common non-haematological side effects are gastrointestinal including nausea, vomiting and anorexia, and respiratory (mainly cough, infection and bronchospasm). With haematological toxicity, severe, prolonged neutropenia was associated with an increase in the infection rate.¹³

A drug warning was issued in October 2005 from the manufacturers, relating to severe cutaneous or mucocutaneous reactions, some with a fatal outcome. These have been reported in the post-marketing experience.

Patients experiencing these reactions should not receive any further component of the ibritumomab regimen and should seek prompt medical evaluation.¹⁴

Monitoring required in patients receiving ibritumomab includes:

- Weekly full blood counts (including platelet count). These need to be carried out more frequently if the patient is severely cytopenic.
- Observation for signs of cytopenia, complications of febrile neutropenia, and haemorrhage for up to 3 months after end of therapy
- Antibody titres are indicated before treatment in patients who have received other murine-based radioimmunotherapy regimens¹⁵.

DOSAGE, ADMINISTRATION AND COST

Treatment consists of two IV administrations of rituximab and one administration of ⁹⁰Y radiolabelled ibritumomab in the following order;

- Day 1 – IV rituximab infusion (250mg/m²)
- Day 7, 8 or 9 – IV rituximab infusion (250mg/m²) plus ⁹⁰Y – radiolabelled ibritumomab infusion straight afterwards – up to a maximum dose of 1200MBq.⁵

The SPC does not support repeated treatment with ⁹⁰Y – radiolabelled ibritumomab.⁵ ⁹⁰Y radiolabelled ibritumomab should only be handled and administered by qualified personnel with appropriate authorisation for the use and manipulation of radionuclides within a designated clinical setting. Infusions should be administered under the close supervision of an experienced physician, with full resuscitation facilities immediately available.

Ibritumomab is supplied as a kit for radiolabelling with Yttrium-90. The kit, supplied by Schering, does not include the ⁹⁰Y, which must be supplied by the end-user.

The radiolabelled product must be handled and administered by qualified personnel and its preparation, use, transfer, storage and disposal are subject to the regulations and/or appropriate authorisation. Before administration to the patient the end product must be tested for radiochemical purity and if this is less than 95% it should not be administered.⁶

According to Schering, cost per ibritumomab 'set' (Zevalin[®]) is £7,250 plus VAT¹⁶. This cost does not include the radioisotope (Ytracis – Yttrium chloride radioisotope) which is an additional £1,360 plus VAT. Assuming one set is used per patient, total cost is **£8,610** (ex VAT). Current costs of rituximab are: 100mg in 10 mL, £349.25 (2 vials) and 500mg in 50 mL = £873.15 (1 vial) (all costs are exclusive of VAT).¹⁷ Assuming a typical patient has a body surface area of 1.7m², total cost of rituximab per patient for the 2 infusions is **£1,746** (ex VAT).

Assuming that total annual incidence of follicular non-Hodgkin's lymphoma in England and Wales is between 3 – 5 per 100,000¹ and a third of follicular non-Hodgkin's lymphoma patients do not respond to rituximab and are potentially suitable for treatment with ibritumomab (1 – 2 per 100,000), this corresponds to a potential total annual cost of between **£10,356** and **£20,712** per 100,000 population.

PLACE IN TREATMENT

There is limited trial evidence to suggest that ibritumomab may be effective in the treatment of follicular non-Hodgkin's lymphoma patients who have relapsed following rituximab or are refractory to treatment.¹⁸ Good communication and co-ordination between nuclear physics, pharmacy, clinical oncology and haematology departments is also particularly vital for the safe delivery of this medicine.

ARRANGEMENTS FOR PRESCRIBING

Ibritumomab should only be prescribed at specialist centres – i.e. those that have access to specialists in nuclear medicine and haematology and that are equipped to deliver and monitor patients appropriately.

FUTURE DEVELOPMENTS

Longer trial follow up will hopefully provide further information on disease free survival and the durability of the response. As relapse is still common after treatment, there may be a desire for repeat use of this treatment by clinicians in the future. Other possible developments include high dose therapy with stem cell support, combined modality therapy with chemotherapy, and combining ibritumomab with cytokine therapy or unlabeled monoclonal antibodies.⁴

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APPENDIX 1

ANN ARBOR STAGING SYSTEM FOR NHL¹

- Stage I** Involvement of single lymph node region or localised involvement of single extralymphatic organ or site
- Stage II** Involvement of 2 or more lymph node regions or localised involvement of a single associated extralymphatic organ or site at its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm
- Stage III** Involvement of lymph node regions on both sides of the diaphragm that may be accompanied by localised involvement of an extralymphatic organ or site, by involvement of the spleen, or both
- Stage IV** Disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement

APPENDIX 2

SUMMARY OF TRIALS

Key: A/E – adverse effect; CR – complete response; Cru – complete response unconfirmed; DR – duration of response; MC – multicentre; NHL – non-hodgkins lymphoma; ORR: overall response rate; PR – partial response; RCT – randomised controlled trial; TTP – time to progression

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Witzig T E, Flinn I W, Gordon L I et al 2002 ⁴	Single arm, Phase II	Rituximab 250mg/m ² on day 1 and day 8 and ⁹⁰ Y ibritumomab tixetan (0.4mCi/kg [15MBq/kg] on day 8 immediately after the 2nd rituximab infusion	57 (follicular NHL patients = 54)	Patients with follicular B-cell NHL with prior treatment with rituximab, 375mg/m ² for 4 weeks and either didn't respond or had a TTP < 6 months. Patients were 18 years or older and had bidimensionally measurable disease, less than 25% bone marrow involvement with lymphoma	Prior autologous bone marrow transplantation or peripheral blood stem-cell support, prior radioimmunotherapy, or external-beam radiation therapy to more than 25% of active bone marrow	Primary endpoint was a target ORR. Secondary endpoints included TTP and DR.	ORR was 74% (40/54 patients) with 15% (8/54) CR's and 59% (32/54) PR's. Ibritumomab produced tumour shrinkage in 94% (51/54) patients. Median TTP was 6.8 months (1.1≥25.9 months) with 30% data censored. Median TTP in the 40% responders was 8.7 months (1.7≥25.9 months) with 28% of the data censored. Median DR was 6.4 months (0.5 ≥ 24.9 months)	Adverse effects were primarily haematologic and transient - no patient discontinued treatment because of an A/E. Incidence of grade 4 neutropenia, thrombocytopenia and anaemia was 35%, 9% and 4% respectively. The most common non-haematologic A/E were infusion related and were consistent with those described for rituximab. This included asthenia (54%), nausea (35%), chills (25%) and fever (21%). 4 patients were hospitalised.

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Witzig T E, Gordon L I, Cabanillas F et al 2002 ²	Prospective ly RCT, MC, Phase III	Control patients received four once weekly doses of rituximab 375 mg/m ² Rituximab 250mg/m ² on days 1 and 8, 11 in ibritumomab on day 1 and ⁹⁰ Y ibritumomab on day 8 after the day 8 rituximab	70 73	All patients had advanced disease with a median of 2 prior regimens.		Primary endpoint was a target ORR. Secondary endpoints included TTP and DR. Additional efficacy end points were CR rate, complete clinical response rate (CCR), PR rate, time to next anticancer therapy (TTNT) and quality of life (QOL).	ORR was 80% (58/73) in the ⁹⁰ Y ibritumomab (I) group, and 56% (39/70) in the rituximab (R) group (95% CI 68.1-87.7 and 43.4-67.4 respectively) CR was 30% (22/73) and 16% (11/70) respectively, and CCR/Cru was 4% (3/73) and 4% (3/70) respectively. PR was 45% (33/73) and 36% (25/70) respectively.	Higher incidences of grades 1 and 2 cough (15% vs 7%), bronchospasm (6% vs 4%), dyspnoea (15% vs 7%) and for grades 1 and 2 nausea (43% vs 19%), vomiting (19% vs 7%) and anorexia (11% vs 3%) for ⁹⁰ Y ibritumomab compared to the rituximab group. 5 patients (7%) in the ⁹⁰ Y ibritumomab group were hospitalized with infection or febrile neutropenia. All recovered.
Follow up to above trial Gordon L I, Witzig T E, Molina A et al 2004 ⁸	MC, 2 arm, RCT Phase III	As Above	As Above	As Above		As Above	CR & Cru were 34% in I arm and 20% in R arm respectively (P=0.04). In follicular NHL patients, comparing I to R, TTP was 15 vs 10.2 months (P=0.07) respectively, DR was 16.7 vs 11.2 months (P=0.44) respectively and TTNT was 21.1 vs 13.8 months (P=0.27) respectively. (This trial was not powered to detect this though)	As Above

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Gordon L I, Molina A, Witzig T E et al 2004 (Brief Report) ⁹	Single arm, dose escalation study. Phase 1/2. Follow up study	Dosages were: 0.2, 0.3 and 0.4 mCi/kg (7.4 MBq/kg). Dose capped at 32 mCi (1184 MBq/kg)	51	Patients with histologically confirmed, relapsed or refractory low-grade or follicular B-cell NHL who had failed 2 prior regimens or 1 anthracycline containing regimen.	Not stated	Primary endpoint was ORR. Secondary endpoints were TTP and DR	ORR in all patients was 73% (51% CR/Cru, 22% PR). In follicular patients ORR was 85%. DR was 11.7 months (0.7-74.3+) and TTP was 9.3 months (0.9-75.5+)	Previously described. 4% of the patients developed myelodysplastic syndrome 2 to 3 years after ibritumomab.
Wiseman G A, Gordon L I, Multani P S et al 2002 ¹⁰	Open label, single arm, MC phase II study	Initial infusion of rituximab and injection of 111In ibritumomab for dosimetry followed 1 week later with rituximab and ⁹⁰ Y ibritumomab (0.3mCi/kg[11MBq/kg])	30	Over 18 years, with histologically confirmed, relapsed or refractory low-grade follicular or transformed CD20+ NHL. Patients had mild thrombocytopenia, absolute neutrophil count 1.5 x 10 ⁹ cells/L or more, and total lymphocyte count of more than 5 x 10 ⁹ cells/L	Not stated	Primary endpoint was the ORR in intent to treat patients. Secondary endpoints included CR rate, PR rate, TTP and DR	ORR of 83% was seen in 25/30 intent to treat patients. CR was achieved in 37% (11 patients), Cru in 6.7% (2 patients) and PR in 40% (12 patients). Follicular patients had ORR of 92%. Median TTP was 9.4 months (1.7-24.6). Median DR was 11.7 months (3.6-23.4)	33% (10 patients) had grade 4 neutropenia, 13% (4 patients) had grade 4 thrombocytopenia and 3% (1 patient) had grade 4 anaemia. Other A/E included ashenia (50%), nausea (40%), chills (37%), vomiting (30%), fever (30%) and headache (27%). 96% of A/E were grades 1 or 2.

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