

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

**THE USE OF IBRITUMOMAB AS
CONSOLIDATION THERAPY AFTER
REMISSION INDUCTION IN PREVIOUSLY
UNTREATED FOLLICULAR 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 (Newcastle). 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 rest 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
The use of azacitidine for the management of myelodysplastic syndromes	May 2009
The use of aprepitant for the prevention of chemotherapy induced nausea and vomiting	March 2009
Current therapeutic strategies for pulmonary arterial hypertension	March 2009
The use of lapatinib in the management of metastatic breast cancer	November 2008
The use of liposomal doxorubicin in the management of metastatic breast cancer	October 2008
The use of dasatinib in the management of acute lymphoblastic leukaemia in adults	August 2008
The use of bevacizumab in the management of metastatic breast cancer (N)	September 2007
The use of entecavir in the management of chronic hepatitis B infection (N)	March 2007
The use of natalizumab in the management of multiple sclerosis (N)	March 2007
The use of aromatase inhibitors in the treatment of early stage breast cancer (N)	March 2007
Palonosetron for the prevention of nausea and vomiting associated with cancer chemotherapy	March 2007
Alemtuzumab in the management of chronic lymphocytic leukaemia	March 2007
Omalizumab in the management of severe, persistent, allergic asthma (N)	June 2006
Bortezomib second-line in the management of multiple myeloma (N)	March 2006
Adjuvant docetaxel or paclitaxel in the management of early stage breast cancer (N)	March 2006
Erlotinib in the management of non-small cell lung cancer (N)	March 2006

Older reports are available via our website or on request

Agents which have been reviewed by the National Institute for Health and Clinical Excellence (NICE) are indicated by **(N)** after the report name. Please refer to the NICE website to access their guidance for these agents/conditions.

Regional Drug and Therapeutics Centre
Wolfson Unit
Claremont Place
Newcastle upon Tyne NE2 4HH
Telephone: 0191 232 1525 / Fax: 0191 260 6192
E-mail: nyrdtc.dj@ncl.ac.uk
Website: www.nyrdtc.nhs.uk

SUMMARY

- Follicular lymphomas are the most common type of non-Hodgkin's lymphoma (NHL), accounting for about 25% of all cases. In England in 2006, 4,731 and 4,037 new cases were diagnosed in men and women, respectively. The annual incidence of follicular lymphoma is between 3 and 5 per 100,000 and the prevalence is about 40 per 100,000. Follicular lymphomas are low grade and usually develop slowly.
- Ibritumomab is a monoclonal antibody attached to a radioisotope (⁹⁰Yttrium). Radiation is specifically targeted to CD20+ cells, while normal non-lymphoid cells are spared.
- Ibritumomab is licensed as consolidation therapy after remission induction in previously untreated patients with follicular lymphoma. It was originally approved in 2004 for the treatment of adults with rituximab-relapsed or refractory CD20+ follicular B-cell NHL. This review considers the former indication only.
- The Scottish Medicines Consortium has not recommended ibritumomab for use on this indication in Scotland. Ibritumomab is not on the work programme of NICE, which has considered rituximab, and approved it as an option for treating stage III and IV follicular lymphoma in previously untreated patients.
- A phase III study evaluating consolidation therapy with ibritumomab has been published. Following induction, patients were randomised either to a control arm (n = 206) and received no further treatment or an active arm (n = 208), in which patients received one rituximab infusion, with the second infusion a week later followed by ⁹⁰Y-ibritumomab tiuxetan 14.8 MBq/kg. Primary endpoint was progression-free survival (PFS). Secondary endpoints included, amongst others, PFS based on type of induction therapy, overall survival (OS) and safety.
- Median PFS was 13.3 months in the control arm and 36.5 months in the ibritumomab arm (hazard ratio (HR) 0.465, 95% confidence interval (CI) 0.357 to 0.605; p < 0.0001). Only 31 and 28 patients respectively had had rituximab in their induction regimens (14.3% overall). Significantly improved PFS was not achieved in these patient groups (HR 0.722, 95% CI 0.304 to 1.714; p = 0.4583). At current follow-up (3.5 years) there is no significant difference in OS.
- The most common adverse events (AEs) were haematological, including grade 3 lymphopenia (60.3%), neutropenia (grade 3 - 40.2%, grade 4 - 26.5%) and thrombocytopenia (grade 3 - 58.8%, grade 4 - 2.0%). The overall incidences of non-haematological and haematological AEs were 80.0% and 14.6% for the control arm and 95.1% and 72.5% for the ibritumomab arms, respectively.
- There is a potential total annual treatment cost of between £21,426 and £42,852 per 100,000 population.
- Further trial analysis is needed before ibritumomab can be recommended for use as consolidation therapy in patients with previously untreated follicular lymphoma. In particular, it is important to ascertain whether patients who have received rituximab as induction therapy benefit from treatment with ibritumomab, and whether there is any improvement in overall survival over a longer period of time.

BACKGROUND

Follicular lymphomas are the most common type of non-Hodgkin's lymphoma (NHL),¹ accounting for about 25% of all NHL, and are cancers of the B lymphocytes.² In England in 2006, 4,731 new cases of NHL were diagnosed in men and 4,037 in women and accounted for 2.8% of all diagnosed cancers. Of these, 680 (14.4%) and 768 (19.0%) respectively were follicular NHL.³ The annual incidence of follicular lymphoma is between 3 and 5 per 100,000 and the prevalence is about 40 per 100,000.⁴

Follicular lymphomas are classified as low-grade lymphomas and usually develop slowly.² There are a wide range of current treatments for follicular lymphoma, including chlorambucil, CVP (cyclophosphamide, vincristine and prednisolone) CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), rituximab and fludarabine.⁵ The main aim of treating follicular lymphoma is to achieve remission.

Ibritumomab tiuxetan (Zevalin[®], Bayer PLC) is a monoclonal antibody (ibritumomab) attached by a chelating agent (tiuxetan) to a radioisotope (⁹⁰Yttrium).⁶ It is designed to deliver radiation to lymphoma cells by targeting the CD20 antigen which is unique to B-lymphocytes.⁶ Ibritumomab is the parent anti-CD20 antibody that was engineered in the development of rituximab. Thus, the antibody specifically targets radiation to CD20+ cells while sparing normal non-lymphoid cells.⁷

Patients are pre-treated with an infusion of unlabelled rituximab seven days before ibritumomab treatment. The reason for this is it is thought to remove normal cells carrying the CD20 antigen from the peripheral blood system and therefore radioactivity is stopped from being distributed throughout the body. On the eighth day, ibritumomab is given as a slow intravenous infusion, following a second infusion of rituximab.⁶

Ibritumomab was approved in 2004 for the treatment of adults with rituximab-relapsed or refractory CD20+ follicular B-cell NHL.⁸ In May 2008, the licence was extended to include its use as consolidation therapy after remission induction in previously untreated patients with follicular lymphoma.⁹ The benefit of ibritumomab following rituximab in combination with chemotherapy has not been established.¹⁰ Consolidation therapy is a cancer treatment that is given following induction therapy (usually chemotherapy) with the aim of improving the initial effect of the induction therapy.⁸

CURRENT GUIDANCE

The Scottish Medicines Consortium (SMC) reviewed ibritumomab in July 2008,¹¹ and concluded:

“Ibritumomab tiuxetan (Zevalin[®]) is not recommended for use within NHS-Scotland as consolidation therapy after remission induction in previously untreated patients with follicular lymphoma.

The holder of the marketing authorisation has not made a submission to SMC regarding the product in this indication. As a result we cannot recommend its use within NHS-Scotland.”

It was therefore not approved due to a lack of submission by the manufacturer only; clinical and cost analyses were not carried out.

Ibritumomab has not been assessed by NICE (National Institute for Health and Clinical Excellence) and is not currently on the work programme. NICE assessed rituximab for the treatment of follicular lymphoma in September 2006,⁵ and recommended that:

“Rituximab, within its licensed indication (that is, in combination with cyclophosphamide, vincristine and prednisolone) is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated patients.”

NICE has also assessed rituximab for relapsed or refractory stage III or IV follicular NHL,¹² and recommended that:

In people with relapsed stage III or IV follicular NHL, rituximab is now an option in combination with chemotherapy to induce remission or alone as maintenance therapy during remission. Rituximab monotherapy is also an option for people with relapsed or refractory disease when all alternative treatment options have been exhausted.

This review will only consider the use of ibritumomab as consolidation therapy after remission induction in previously untreated patients.

EFFICACY

PHASE III STUDY

A phase III, multicentre, open-label, randomised controlled trial was published in November 2008.¹³

The trial was designed to evaluate the safety and efficacy of consolidation therapy with ibritumomab in patients who had achieved a partial response (PR) or better with a first-line initial chemotherapy regimen.

Patients had confirmed grade 1 or 2 follicular lymphoma, were stage III or IV at diagnosis and had a WHO (World Health Organisation) performance status of 0 to 2. They needed to have had either a PR or complete (CR) or unconfirmed complete (CRu) response after receiving first-line chemotherapy. This initial induction therapy included either chlorambucil, CVP, CHOP, CHOP-like, fludarabine combinations or rituximab combinations. A relatively high number of patients screened were included in the trial (414 out of 502 patients, 82.5%), and only a minority (n = 88) were excluded (most due to not being eligible, n = 69). A total of 206 patients were assigned to the control arm (no further treatment) and 208 to the ibritumomab arm. Patients were evenly balanced between the two arms and the sample size was appropriate for the primary endpoint. Of these patients, 199 and 200 respectively, completed the trial. The efficacy evaluations were based on the intention to treat population (n = 206 and n = 208) and the safety evaluations were based on those who had post-baseline data available (205 and 204 patients in the control and treatment arms respectively). All patients were accounted for.

The 206 patients in the control arm received no further treatment. The 208 actively treated patients received one rituximab infusion (250 mg/m²) alone, with the second a week later, followed immediately by ⁹⁰Y-ibritumomab tiuxetan 14.8 MBq/kg administered by slow IV injection. Blinding was not possible due to the different regimens.

The primary endpoint was overall progression-free survival (PFS) and PFS stratified by response to first line induction chemotherapy (PR or CR/CRu). PFS was calculated from the date of treatment assignment to the date of relapse, disease progression or death from any cause.

Secondary endpoints included PFS based on type of first-line induction therapy, PFS according to Follicular Lymphoma International Prognostic Index (FLIPI) scores, improvement in CR rate, conversion rate to *bcl-2* polymerase chain reaction-negative status in the blood, overall survival (OS) and safety.

RESULTS

The results obtained following the median observation time of 3.5 years are shown in table 1.¹³

TABLE 1 – RESULTS FROM THE PHASE III TRIAL

Endpoint	Control arm (n = 206)	Ibritumomab arm (n = 208)	Statistical analysis
Median PFS	13.3 months	36.5 months	HR* 0.465, 95% CI** 0.357 to 0.605, p < 0.0001
Median PFS in PR patients following induction	6.2 months	29.3 months	HR 0.304, 95%CI 0.213 to 0.434, p < 0.0001
Median PFS in CR/CRu patients following induction	29.5 months	53.9 months	HR 0.613, 95%CI 0.410 to 0.914, p = 0.0154
Conversion to CR/CRu from PR after consolidation	17 out of 97 (17.5%)	78 out of 101 (77%)	p < 0.001
Final CR/CRu rate	53.3%	87.4%	

*HR – Hazard ratio; **CI – Confidence interval

With regards the secondary endpoint of OS, at current follow up (3.5 years) there was no difference reported between the two arms.¹³ One of the secondary endpoints was the number of patients who converted to CR/CRu from PR after ibritumomab treatment. There was a statistically significant difference between the arms with 77% of the ibritumomab arm converting compared to 17.5% in the control arm. The trial was not powered to show a difference but the results are nevertheless, interesting.

The authors of the trial performed a subgroup analysis, comparing chemotherapy regimens that were administered as first-line induction therapy. It is important to be aware that the trial was not powered to show a difference between the various first-line chemotherapy regimens. These results are shown in table 2:

TABLE 2 – MEDIAN PFS ACCORDING TO FIRST-LINE REGIMEN

First line Regimen	Control - PFS (n = 206)	Ibritumomab - PFS (n = 208)	Statistical analysis
Chlorambucil	11.9 months (n = 19)	Not reached (n = 20)	HR 0.344, 95% CI 0.150 to 0.793, p = 0.0088
CVP/COP	7.9 months (n = 53)	28.5 months (n = 53)	HR 0.383, 95% CI 0.235 to 0.625, p = 0.0001
CHOP	12.5 months (n = 61)	35.9 months (n = 66)	HR 0.391, 95% CI 0.246 to 0.622, p < 0.0001
CHOP – like	29.2 months (n = 31)	Not reached (n = 30)	HR 0.474, 95% CI 0.219 to 1.029, p = 0.0533
Fludarabine combination	24.3 months (n = 11)	41.4 months (n = 11)	HR 0.884, 95% CI 0.283 to 2.769, p = 0.8332
Rituximab combination	Not reached (n = 31)	Not reached (n = 28)	HR 0.722, 95% CI 0.304 to 1.714, p = 0.4583

The above table shows that only 13.5% of patients in the ibritumomab arm received a rituximab combination as part of their induction chemotherapy regimen (14.3% overall). The opinion in the North of England is that a rituximab containing regimen is the preferred first line regimen.¹⁴⁻¹⁶ The choice of induction therapy is of particular relevance as NICE has approved rituximab in combination with CVP as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated patients.⁵ The small number of patients in this subgroup will affect the general applicability of the trial results as a whole to the UK population. This trial was not powered to show efficacy of ibritumomab in this specific population and there is inadequate data available to assess this. The data in table 2 shows that PFS was not reached in either group (p = 0.4583).¹³ A recent review has confirmed the benefits of rituximab-containing chemotherapy regimens as induction therapy.¹⁷

A phase II non-randomised trial studied the effects of fludarabine and mitoxantrone followed by ibritumomab in previously untreated patients with follicular NHL.¹⁸ Sixty-one patients were enrolled and 57 were eligible to receive ibritumomab consolidation therapy. After a median follow-up of 30 months, estimated PFS was 76% (95% CI 72.3 to 82.4) and estimated three-year OS was 100%.

One phase II trial update, published in abstract form in 2005, studied the combination of rituximab with CHOP, followed by ibritumomab as first-line treatment in patients with follicular lymphoma. Following the induction chemotherapy, all patients responded (28% CR and 72% PR). After ibritumomab was administered, the CR rate improved to 67%. Myelosuppression resolved by 12 weeks in all patients.¹⁹

Further analysis in clinical trials is needed; considering a population of patients who have received rituximab as part of their induction chemotherapy before we can be sure of the benefits, or otherwise, of ibritumomab in this population.

This is particularly relevant in a United Kingdom population who may well receive rituximab as induction chemotherapy.

ADVERSE EFFECTS

The most commonly reported grade 3 or 4 adverse events (AEs) in the phase III study were haematological.¹³ The overall frequencies of any AE were 165 (80.5%) patients in the control arm and 201 (98.5%) patients in the ibritumomab arms.²⁰ The overall incidences of non-haematological AEs and haematological AEs were 80.0% and 14.6% for the control arm and 95.1% and 72.5% for the ibritumomab arm, respectively. The majority of non-haematological AEs were grade 1 or 2 (60% and 65% of the AEs in the control and ibritumomab arms, respectively). Grade 3 or 4 AEs occurred in 19.1% of the control group and 28.9% of the ibritumomab arm, respectively.²⁰ The most common grade 3 and 4 AEs are shown in more detail in table 3 below:^{13,20}

TABLE 3 - GRADE 3 OR 4 ADVERSE EVENTS IN THE PHASE III TRIAL

Adverse-Event	Control arm (n = 205) n (%)		Ibritumomab arm (n = 204) n (%)	
	Grade 3	Grade 4	Grade 3	Grade 4
Lymphopenia	22 (10.8%)	0	123 (60.3%)	0
Neutropenia	4 (2.0%)	1 (0.5%)	82 (40.2%)	54 (26.5%)
Thrombocytopenia	0	0	120 (58.8%)	4 (2.0%)
Anaemia	0	0	6 (2.9%)	1 (0.5%)
Infections	5 (2.4%)	0	14 (6.9%)	2 (1.0%)
Gastrointestinal	2 (1.0%)	Not Reported	8 (3.9%)	Not Reported
Vascular disorders		Not Reported	10 (4.9%)	Not Reported
General disorders & administration site conditions		Not Reported	10 (4.9%)	Not Reported
Pyrexia	0	0	5 (2.5%)	1 (0.5%)
Hypertension	1 (0.5%)	0	6 (2.9%)	0
Respiratory & mediastinal	1 (0.5%)	Not Reported	6 (2.9%)	Not Reported

Of the 76 patients in the ibritumomab arm who suffered a serious AE, 53 experienced at least one that was thought to be related to the treatment.²⁰ None of the control arm serious AEs was considered treatment-related. After a median of 3.5 years, 11 patients had died.¹³ Five patients died in the control arm due to sepsis (n = 1) and progressive disease (n = 4). The six patients in the ibritumomab arm died due to neutropenic sepsis after subsequent chemotherapy (n = 1), pancreatic cancer (n = 1), acute myeloblastic leukemia (n = 1) and progressive disease (n = 3).

Haematological AEs during the trial were managed in various ways. A total of 36 patients with grade 3 or 4 neutropenia received growth factor support and 42 received platelet transfusions.¹³ Four out of seven patients with grade 3 or 4 anaemia received red blood cell transfusions.

The most common AE is myelotoxicity. The EMEA regarded this AE as being “serious, but manageable”.²⁰

DOSAGE, ADMINISTRATION AND COST

Treatment with ibritumomab consists of:

Day 1 – First IV rituximab infusion (250 mg/m²)

Days 7, 8 or 9 – Second IV rituximab infusion (250 mg/m²) shortly before ⁹⁰Y-radiolabelled ibritumomab

The ⁹⁰Y-radiolabelled ibritumomab infusion is given over 10 minutes up to a maximum dose of 1200 MBq.¹⁰

The Summary of Product Characteristics (SPC) does not support repeated treatment with ⁹⁰Y – radiolabelled ibritumomab as data on re-treatment are not available. (The SPC advises that ⁹⁰Y-radiolabelled ibritumomab should only be administered by qualified personnel who have the appropriate authorisation to use and manipulate radionuclides in a clinical environment.) When the infusion is being administered, resuscitation facilities should be available and an experienced physician should be supervising.¹⁰

Ibritumomab is supplied as a kit for radiolabelling with Yttrium-90. The kit, supplied by the manufacturer, 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 strict 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.

According to Bayer, the cost per ibritumomab ‘set’ (Zevalin[®]) is £6,967 plus VAT.²¹ This cost does not include the radioisotope (Ytracis[®] – Yttrium chloride radioisotope) which is an additional £2,000 approximately.²¹ Assuming one set is used per patient, the total cost per patient is **£8,967** (excl VAT). Current costs of rituximab are: 100 mg in 10 ml, £349.25 (2 vials) and 500 mg in 50 ml = £873.15 (1 vial) (all costs are exclusive of VAT). Assuming a typical patient has a body surface area of 1.7m², the total cost of rituximab per patient for the two infusions is **£1,746** (excl VAT).²²

Assuming that the total annual incidence of follicular non-Hodgkin’s lymphoma in England and Wales is between 3 – 5 per 100,000 and if 82.5% are potentially suitable for treatment with ibritumomab (taken from the percentage in the phase III trial that were eligible for assignment, i.e. 2 – 4 per 100,000), this corresponds to a potential total annual treatment cost of between **£21,426** and **£42,852** per 100,000 population.

PLACE IN TREATMENT

The phase III study that was pivotal in gaining the extension of the licence for ibritumomab was a well structured study. The primary endpoint of improved PFS was met, with an increase in PFS in the ibritumomab arm of over 23 months compared to control (HR 0.465, 95% CI 0.357 to 0.605, $p < 0.0001$). Conversion from PR to CR was a secondary endpoint and as such, the trial was not powered to detect a difference however there was a notable better outcome in the treatment arm. Further data will hopefully become available in the future. There were however some caveats to the trial results. OS has still not been established, and further time is needed to assess whether an improvement will be seen. A further concern is the small percentage of patients in the trial who had received rituximab as their induction chemotherapy (14.3%). It is important to remember that the trial was not powered to show a difference in PFS, according to the induction chemotherapy regimen the patient received. With NICE guidance in England and Wales recommending rituximab as an option in previously untreated patients, this is the patient population in which ibritumomab is most likely to be used. The subgroup analysis did not show a significant difference in PFS (according to induction regimen) between the two arms, but the patient numbers were small ($n = 31$ and $n = 28$ received a first-line regimen including rituximab in the control and ibritumomab groups, respectively). More research is needed to evaluate whether there are additional benefits to adding ibritumomab as consolidation therapy in patients who have received rituximab.

Adverse events were largely haematological in the ibritumomab arm, and while many were grades 3 and 4, and considered serious, they were also felt to be manageable.

Ibritumomab is a specialist product and good communication and co-ordination between nuclear physics, pharmacy, clinical oncology and haematology departments is vital for the safe delivery of this medicine.

In summary, further studies are needed before ibritumomab can be recommended as consolidation therapy in patients with previously untreated follicular lymphoma. Whether an increase in progression-free survival translates into an increase in overall survival with ibritumomab compared to control therapy over a longer period of time, and whether patients who have received rituximab as induction therapy benefit from treatment with ibritumomab, remains to be determined. This is particularly important in a UK population who may well have received rituximab as part of their induction chemotherapy.

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

Studies comparing rituximab-CVP for induction chemotherapy followed by ibritumomab as consolidation treatment are ongoing and the results will be vital in assessing the benefits for the UK population.¹⁷ The PRIMA study has completed internationally and is a multicentre, phase III study in advanced follicular lymphoma patients evaluating the benefits of maintenance therapy with rituximab after induction of response with chemotherapy plus rituximab in comparison with no maintenance therapy.²³ This trial should be reporting in the next few years.¹⁴

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SUMMARY TABLE OF KEY STUDY

NHS

The use of Ibritumomab as consolidation therapy in follicular lymphoma

APPENDIX 2. SUMMARY TABLE OF KEY STUDY

Abbreviations: AE – adverse event, BSC – best supportive care; CI – confidence interval; CNS – central nervous system; CR – complete response, CRu – unconfirmed complete response; FLIPI – follicular lymphoma international prognostic index; HR – hazard ratio; MC – multicentre, PCR – bcl-2 polymerase chain reaction; PFS – progression-free survival, OL – open label; OS – overall survival; PR – partial response; RCT – randomised, controlled trial; WHO – World Health Organisation

Trial	Design	Endpoints	Inclusion criteria	Exclusion criteria	Results	Adverse Effects
Morschhauser F et al. ¹³	MC, RCT, OL, phase III trial 206 patients in the control arm received no further treatment. 208 actively treated patients received one rituximab infusion (250 mg/m ²) alone, with the second a week later, followed immediately by ⁹⁰ Y-ibritumomab tiuxetan 14.8 MBq/kg.	Primary endpoint was overall PFS and PFS stratified by response to first-line induction therapy. Secondary endpoints were PFS based on type of first-line induction therapy, PFS according to FLIPI scores, improvement in CR rate, conversion rate to PCR-negative status, OS and safety.	Age ≥ 18 years, CD20+ confirmed grade 1 or 2 follicular lymphoma, stage III or IV disease at diagnosis, WHO performance status of 0 to 2, achieved a CR/CRu or PR after first-line therapy with the last dose administered 6-12 weeks before start of study, < 25% bone marrow involvement, absolute neutrophil count of ≥ 1.5 X 10 ⁹ /L, haemoglobin levels ≥ 9 g/dL and platelet count ≥ 150 X 10 ⁹ /L.	Patients who received prior radiation therapy or myeloablative therapy, had symptomatic CNS lymphoma or known HIV positivity, total bilirubin > 1.5 x upper limit of normal, or ALT levels > 2.5 x the upper limit of normal.	Median PFS was 36.5 months in the ibritumomab arm and 13.3 months in the control arm (HR=0.465; 95% CI 0.357 to 0.605, p < 0.0001). Median PFS for PR patients after induction therapy was 29.3 months in ibritumomab arm and 6.2 months in control arm (HR 0.304, 95% CI 0.213 to 0.434, p < 0.0001) Median PFS in CR/CRu patients after induction was 53.9 and 29.5 months respectively (HR 0.613, 95% CI 0.410 to 0.914, p = 0.0154) At current follow up (3.5 years), there was no difference in OS between the two arms.	The most common grade 3 and 4 AEs were haematological -lymphopenia 60.3% vs 10.8%, neutropenia 66.7% vs 2.4%, thrombocytopenia 60.8% vs 0% and anaemia 3.4% vs 0% for ibritumomab and control arms respectively. 6.9% vs 2.4% in the ibritumomab and control arms respectively had grade 3 infections, with 5.4% and 5.9% with grade 4 infections. The most frequent grade 1 & 2 non-haematologic AEs affecting > 10% patients in the ibritumomab arm were fatigue (32.8%), nasopharyngitis (19.1%), nausea (18.1%), asthenia (14.2%), arthralgia (11.8%), cough (11.3%), headache (11.3%), diarrhoea (10.8%) and pyrexia (10.3%) After observation for 3.5 years, 11 patients died, 6 in the ibritumomab arm and 5 in the control arm.