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A phase II trial of short course fludarabine, mitoxantrone, rituximab followed by ^{90}Y-ibritumomab tiuxetan in untreated intermediate/high-risk follicular lymphoma

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Background: A prospective, single-arm, open-label, multicenter, nonrandomised phase II trial to evaluate efficacy and safety of short fludarabine, mitoxantrone, and rituximab (FMR) induction followed by radioimmunotherapy, in untreated, intermediate/high-risk follicular non-Hodgkin's lymphoma (NHL) patients.

Patients and methods: Fifty-five patients were treated using a sequential treatment schedule of four induction cycles of FMR chemoimmunotherapy, and a subsequent consolidating single administration of ^{90}Y-ibritumomab tiuxetan (^{90}Y-IT), 8–14 weeks later. Patients were eligible for radioimmunotherapy if at least in partial response (PR) after induction, with normal platelet and granulocyte counts and a bone marrow infiltration ≤25%. Primary study end points were response rate and hematologic toxic effects; secondary end points were overall survival (OS) and progression-free survival (PFS).

Results: All the 55 patients received four induction cycles with an overall response rate of 96% (38 complete responses [CR] and 15 PR). Fifty-one patients (38 in CR and 13 in PR) received ^{90}Y-IT. By the end of the treatment,

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49/55 patients achieved a CR. With a median follow-up of 21 months, the estimated 3-year PFS was 81% and the 3-year OS 100%.

Conclusions: This study has established feasibility, tolerability, and efficacy of a regimen composed by short FMR induction with ^{90}Y-IT consolidation in untreated intermediate/high-risk follicular NHL patients.

Key words: fludarabine, follicular lymphoma, mitoxantrone, radioimmunotherapy, rituximab, ^{90}Y-ibritumomab tiuxetan

introduction

The first choice initial treatment of patients with indolent non-Hodgkin's lymphomas (NHLs) who are not eligible for clinical trials has historically included either alkylating-based regimens—e.g. CVP (cyclophosphamide, vincristine, and prednisolone)—or purine analogues, such as fludarabine. Although more aggressive regimens—e.g. CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolone)—have been used in the initial treatment of follicular lymphoma, there is no evidence of a superior response rate or duration of remission compared with CVP [1]. Fludarabine-based regimens are highly effective but not superior to CVP in terms of remission duration or overall survival (OS) [2].

The treatment paradigm for treating advanced-stage follicular lymphoma has changed with the use of the anti-CD20 monoclonal antibody, rituximab (R). The first phase II study regarding a combination of chemotherapy (CHOP) and rituximab was presented by Czuczman et al. [3] in patients with untreated follicular lymphoma. Phase III randomized trials have then demonstrated a significant improvement in outcome by combining chemotherapy regimens with rituximab [4–6].

Radioimmunotherapy has emerged as an important treatment option for patients with B-cell NHL. Ibritumomab is a murine monoclonal immunoglobulin G1/ kappa antibody directed to CD20, a surface antigen that is expressed on 90% of B-cell lymphomas [7]; it is conjugated to the metal chelator tiuxetan for the retention of the beta emitter ^{90}Yttrium.

In the initial phase I-II trial of ^{90}Yttrium-ibritumomab tiuxetan (^{90}Y-IT), responses were seen in 28 (82%) of the 34 patients with pretreated indolent NHL [8]. Witzig et al. [9] compared ^{90}Y-IT with a standard dose of rituximab in a randomized controlled phase III study in relapsed or refractory indolent follicular NHL, showing statistically significant higher overall response and complete response (CR) rates.

Following reports have confirmed the safety and efficacy of ^{90}Y-IT in pretreated patients with follicular NHL [10, 11]. Moving from these results, further investigations have monitored the role of radioimmunotherapy (using ^{131}I-tositumomab or ^{90}Y-IT) as a consolidation treatment after a chemotherapy induction [12–14] in follicular NHL patients. More specifically, the sequential treatment was represented by fludarabine alone [12] or by a fludarabine-containing regimen [13] followed by ^{90}Y-IT; a CHOP-based chemotherapy induction was instead used by Press et al. [14], followed by ^{131}I-tositumomab administration. The initial reports from these studies have demonstrated the feasibility, tolerability, and efficacy of the combination regimens, being the induction phase represented by chemotherapy, without the addition of rituximab. A recent randomized trial has demonstrated a marked improvement in progression-free survival (PFS) if ^{90}Y-IT is administered after chemotherapy, as part of a front-line treatment [15].

Recently, this innovative approach combining induction chemotherapy and subsequent consolidation with ^{90}Y-IT has been upgraded by the shortening of chemotherapy duration (trying to decrease the potential long-term toxic effects of antiblastic drugs), and—at the same time—by the insertion of rituximab in any chemotherapy regimen [16–18].

In force of these findings, and on the basis of our previously published report on the 'FLUMIZ' study [13], we have decided to investigate the efficacy and safety of the combination of a short course (four cycles instead of six) of fludarabine, mitoxantrone, and rituximab (FMR) followed by a single infusion of ^{90}Y-IT, in untreated intermediate/high-risk follicular NHL patients.

patients and methods

patients

Patients aged ≥18 with biopsy-proven, bidimensionally measurable, stage III or stage IV follicular grade 1–2 NHL expressing the CD20 antigen were considered eligible for this prospective, single-arm, open-label, multicenter (three major Italian cooperative institutions) nonrandomised phase II trial. Patients were to be previously untreated and with clear indication to therapy; they should have a World Health Organization (WHO) performance status of two or less and a Follicular Lymphoma International Prognostic Index (FLIPI, [19]) score ≥2.

All diagnostic biopsies were reviewed by an expert pathologist (SP) in accordance with the WHO classification [20]. All patients had either a follicular or a follicular and diffuse pattern, typically expressing the CD10$^+$, Bcl-6$^+$, and Bcl-2$^+$ phenotype. None of the specimen was IRF4$^+$. The Ki-67 value ranged from 5% to 20%.

All the patients underwent a full medical history; a physical examination; complete blood cell and platelet counts; a computed tomography (CT) scan of neck, chest, abdomen and pelvis (with and without contrast); a whole-body ^{18}F-fluorodeoxyglucose-positron emission tomography (PET) scan, and a bone marrow aspiration and biopsy. Disease stage was established according to the Ann Arbor staging system. Bulky disease was defined as the presence of a nodal or extranodal mass ≥10 cm on its major diameter, as documented on CT scan. Patients were also tested for serum creatinine, liver function tests (including hepatitis-B virus antigens, and hepatitis-C virus antibodies), uric acid, lactate dehydrogenase, human immunodeficiency virus, and underwent urinalysis and electrocardiography. Patients with a history of impaired cardiac status were evaluated by echocardiography and were considered eligible if the cardiac ejection fraction was within normal ranges.

All patients were notified of the investigational nature of this study and signed a written informed consent approved in accordance with

institutional guidelines, including the Declaration of Helsinki. The study was approved by the institutional review board.

treatment plan

Standard i.v. fludarabine (25 mg/m^2 on days 2–4) and mitoxantrone (10 mg/m^2 on day 2) regimen, with the addition of rituximab (375 mg/m^2 on day 1) was administered on a 28 day-schedule for four cycles.

If there had been <1500/μl granulocytes or <100 000/μl platelets by the time the next cycle was due, treatment should have been delayed for 1 week and blood counts repeated. If blood counts had not recovered after 2 weeks, the patient should have been treated at the 75% of the last dose received. A subsequent dose reescalation could have been considered at the discretion of the treating physician. Granulocyte colony-stimulating factor (G-CSF) was not administered to prevent neutropenia, but patients with grade 3–4 neutropenia or neutropenic fever between cycles were allowed to receive growth factors, at the physician's discretion.

Two to 3 weeks after the completion of the fourth cycle of FMR regimen, patients were restaged by physical examination, blood tests, CT scan, PET scan, and bone marrow aspiration and biopsy. Patients in at least a partial response (PR) were considered eligible for consolidation therapy with ^{90}Y-IT, provided their granulocyte counts were greater than 1.5×10^9/l, platelet counts exceeded 100×10^9/l, and lymphoma bone marrow infiltration was <25% of the total cellularity. Responses were classified according to the revised response criteria for malignant lymphomas [21].

Once the restaging procedures have been fully accomplished, eligible patients received one course of ^{90}Y-IT within 12 weeks. It consisted of an initial infusion of rituximab at 250 mg/m^2 on day 1 and a subsequent infusion at the same dose on day 8 (±1 day); the second infusion of rituximab was then followed by a weight-based dose of ^{90}Y-IT, administered as a slow i.v. push over 10 min. The dose of ^{90}Y-IT was established on 11.1 MBq/kg (0.3 mCi/kg) for patients with pretreatment platelet counts ranging from 100×10^9/l to 149×10^9/l, and on 14.8 MBq/kg (0.4 mCi/kg) for those with counts of 150×10^9/l or higher. In any case, the maximum total dose has never exceeded 1184 MBq (32 mCi). ^{90}Y-IT was routinely administered on an outpatient basis in view of its beta decay, with a complete lack of gamma emissions.

Because of the transitory myelosuppression generally observed after the administration of ^{90}Y-IT, complete blood cell counts with leukocyte differential and platelet counts were carried out in all patients on a weekly basis, from the third week after radioimmunotherapy until the complete hematologic recovery.

Disease status was evaluated again 3 months after radioimmunotherapy through physical examination, bone marrow biopsy (if still positive after induction chemotherapy), CT and PET scan; other clinically relevant information, such as the development of febrile neutropenia, the use of antibiotics or G-CSF or blood transfusion during cytopenia and the presence of any extra-hematologic toxicity, were recorded. Patients' follow-up assessment included: blood count and physical examination every 3–4 months for the first 2 years and then every 6 months for the following 3 years, CT scan every 6 months for the first 2 years, followed by annual imaging studies with CT or PET/CT up to 5 years from treatment completion.

Safety and tolerability were evaluated by monitoring incidence, severity, and type of any adverse event, according to the WHO criteria for toxicity.

molecular monitoring of minimum residual disease

In order to evaluate the molecular response to the treatment in terms of minimal residual disease (MRD), 35 patients enrolled in this trial, who were assessable for Bcl-2 expression in peripheral blood and/or bone marrow aspirate both before and after treatment, have been monitored by qualitative PCR for the presence of *Bcl2-IgH* rearrangement (at the major breakpoint region and at minor cluster region breakpoints) throughout the study, at certain time points: molecular assessment was carried out at diagnosis, after treatment with FMR regimen, and after the infusion of ^{90}Y-IT. Assessment was repeated every 6 months during follow-up. Laboratory procedures and reactants descriptions have been reported elsewhere [13].

Molecular complete response was defined as the absence of *Bcl-IgH* rearrangement in both bone marrow and peripheral blood samples, in atleast two independent repetitions.

statistical analysis

Sample size estimation was carried out by single stage procedure [22]. Previous experience shows that the overall response rate is 50%. Defining π_0 as the proportion of responses below which treatment does not warrant further investigation and π_a as the proportion of responses beyond which a phase III trial should be carried out, we set: $\pi_0 = 0.5$ and $\pi_a = 0.8$. The number of patients needed, given an α error at 0.05 two-sided and a power of $1-\beta = 80\%$, was 55 and the number of successes (overall responses) 40. If, by the end of the trial, at least 40 responses were observed, the treatment regimen would be accepted for a phase III trial [22].

Primary end points were efficacy (measured by overall response rate) and safety (measured in function of grade 3–4 hematologic toxic effects). Secondary end points were OS and PFS.

Overall objective response rate (ORR) is defined as the proportion of patients with complete response (CR) or PR according to revised response criteria for malignant lymphomas [21]. PFS is defined as the time from study entry to the first documentation of objective tumor progression or death due to any cause. OS and PFS curves were plotted by the Kaplan–Meier method [23].

Comparisons were carried out with Pearson's chi-squared test on absolute frequencies and with Wilcoxon test for equality of survivor functions.

The intention-to-treat analysis set was used for all study end points. Demographics and patients' characteristics were summarized by descriptive statistics. Statistical analyses were carried out with Stata 11 (StatCorp LP, College Station, TX) and *P* values were set at 0.05.

This trial is registered as a European Standard Controlled Trial on the EudraCT website http://oss-sper-clin.agenziafarmaco.it, number 2006-004850-26 and at http://ClinicalTrials.gov, ID NCT00859001.

results

Fifty-five patients (25 men and 30 women) were included in the trial at three major Italian cooperative institutions between December 2006 and November 2008, when the study reached completion. Patients' characteristics are listed in Table 1. Median age was 56 years (range 26–84 years) and median time from diagnosis to study entry was 3 months (range 1–6 months). Twenty patients had stage III disease and 35 had stage IV, with bone marrow involvement in 30 cases. Eleven patients presented with bulky disease.

At the time of the first reassessment, i.e. after the four cycles of the FMR induction regimen (Figure 1), the overall response rate was 96%, with 38 out of 55 patients achieving a CR and 15 a PR; the remaining two patients showed progressive disease, being therefore ineligible for further treatment.

Fifty-one patients were deemed eligible for consolidation with ^{90}Y-IT: more specifically, all the patients with metabolic CR and 13 patients with PR (all the PR patients were PET positive). The remaining two patients, both in PR, were excluded from the second part of the treatment program because of a bone marrow infiltration greater than the 25% of cellularity, as documented by a bone marrow biopsy carried out upon this time. There was no evidence of any patient receiving

Table 1. Patients' characteristics (n = 55)

Median age (range) (years)		56 (26–84)
Sex	Male	25
	Female	30
Bulky disease (≥10 cm)	Yes	11
	No	44
Extranodal involvement	Yes	8
	No	47
Stage (Ann Arbor)	III	20
	IV	35
Hemoglobin concentration (g/l)	<120	22
	≥120	33
Number of nodal areas	>4	20
	≤4	35
Increased LDH concentration	Yes	26
	No	29
B-symptoms	Yes	18
	No	37
Bone marrow involvement	Yes	30
	No	25
FLIPI (score)	Intermediate risk (2)	36
	High risk (≥3)	19

B-symptoms: fever, weight loss, night sweats, pruritus *sine materia*.
LDH, lactate dehydrogenase; FLIPI, Follicular Lymphoma International Prognostic Index.

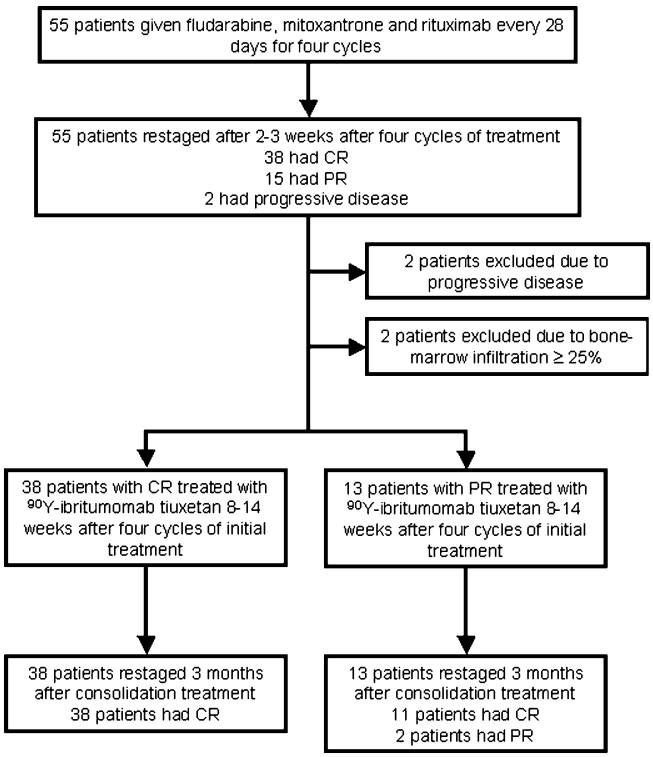

Figure 1. Trial profile.

a reduced dose of ^{90}Y-IT because of persisting thrombocytopenia after FMR.

The CR rate upon completion of the entire treatment regimen (FMR + ^{90}Y-IT) was 89% (consisting of 49 out of 55 patients; 2 patients still maintained their PR status).

The addition of ^{90}Y-IT improved the overall best response (from PR to CR) in 11 of 13 patients who initially achieved PR with FMR only: all of them obtained a cumulative CR (PET negative). At a median follow-up time of 24 months (range 14–38 months), 6 of 55 patients experienced progression. More precisely, the consolidation therapy with ^{90}Y-IT has substantially improved the CR rate: among the 38 patients who had a CR after induction, only 3 (8%) have shown a disease relapse so far, at a median follow-up of 28 months (range 17–41 months). In force of these data, the estimated 3-year PFS is of 81% (95% confidence interval 54–93) and the 3-year OS rate is of 100% (Figure 2).

In terms of molecular monitoring of MRD, 9 patients (26%) out of the 35 tested for Bcl-2 expression showed *Bcl2-IgH* negativity after the fourth cycle of FMR regimen; on the contrary, 26 patients demonstrated a *Bcl2-IgH* positivity, 22 at the major breakpoint region site and 4 at both major breakpoint region and minor cluster region. These 26 cases were then monitored for MRD during the follow-up: 21 patients achieved molecular complete remission, 18 within 6 months after ^{90}Y-IT, and 3 after 12 months. Molecular relapse occurred in two patients at a median follow-up of 20 months (range 12–36 months), without a clinically documented disease relapse.

Regarding the safety profile of the complete regimen, no treatment-related deaths have occurred. The FMR regimen was well tolerated by most of the patients, and reversible hematologic toxic effects were the most common adverse events. No grade 3–4 anemia was noted, whereas grade 3–4 neutropenia was observed in 19 patients, and grade 3–4 thrombocytopenia in 2 patients. Only one patient developed febrile neutropenia. No ^{90}Y-IT infusion-related reactions were reported. Adverse events after radioimmunotherapy were primarily hematologic and transient, and no patient has discontinued treatment because of an adverse event. The severity of the hematologic toxicity (expressed as the lowest—nadir—concentration of granulocytes, platelets, and hemoglobin) and its duration are reported in Table 2. Grade 3–4 thrombocytopenia, neutropenia, and anemia occurred in the 55%, 42%, and 15% of patients, respectively. Twelve (22%) patients received G-CSF, and transfusions of red blood cells, platelets, or both were given to 18 (33%) patients. Four (7%) patients experienced febrile neutropenia, but only one required hospitalization.

No extra-hematologic adverse events have been reported; no patients have shown a thyroid-stimulating hormone elevation, nor any secondary malignancies have occurred.

discussion

This study has established the feasibility, tolerability, and efficacy of a sequential treatment with four cycles of FMR followed by ^{90}Y-IT as a front-line therapy for untreated patients with intermediate/high-risk follicular NHL. These data represent the first evidence of a real role of ^{90}Y-IT after a fludarabine-containing regimen plus rituximab in the treatment of high-risk follicular NHL, thus corroborating the power of a sequential treatment, with the potential benefit of reducing from 6 to 4 induction cycles because it is possible to achieve the same therapeutic results [13] with the possibility, at

the same time, of reducing the cumulative toxicity of the two additional cycles of conventional chemotherapy.

Clinical evaluation of immunotherapy based on anti-CD20 monoclonal antibodies has markedly affected the treatment approach for indolent follicular NHL [4–6, 24, 25]; at the same time, the fluorinated nucleotide analogue fludarabine has demonstrated activity in indolent NHL both as single agent and in combination [26–28]. In parallel, radioimmunotherapy has represented an innovative approach: particularly, ^{90}Y-IT has demonstrated to be one of the most active agents in the treatment of lymphoma, with a manageable toxicity mainly consisting of transient myelosuppression and antibody-associated infusion reactions. Clinical trials with this agent have shown significant activity in pretreated indolent NHL [8–11], including chemotherapy or rituximab-resistant disease. On the basis of these data, further investigations have monitored the role of radioimmunotherapy as a consolidation treatment after chemotherapy induction in follicular NHL patients: benefits in this sense have been shown in a recent phase III trial [15], but also in several phase II trials [13, 16–18], the results of which are summarized in Table 3. Differently from our previous study [13], this trial puts the accent on the use of rituximab in combination with chemotherapy in a short, four-cycle induction phase. In this sense, it differs from other trials [16–18] as follows: i) only intermediate/high-risk patients were included and ii) molecular response was evaluated.

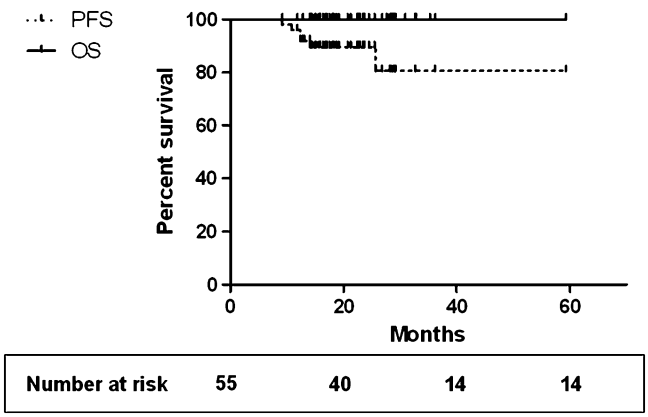

Figure 2. Kaplan–Meier curves for overall survival and progression-free survival with FMR regimen (four cycles) followed by ^{90}Y-ibritumomab tiuxetan in untreated patients with high-risk follicular NHL.

Table 2. Hematologic toxic effects after ^{90}Y-ibritumomab tiuxetan

	Nadir, median (range)	Median duration of grade 3–4 cytopenia* (range), days
Absolute neutrophil count	710, 10^6 cells/l (80–2230)	31 (6–92)
Platelets	21, 10^9 cells/l (5–95)	29 (11–72)
Hemoglobin	98, g/l) (75–139)	30 (18–91)

*Defined as: platelets <50·10^9/l; hemoglobin <80 g/l; neutrophils <1000·10^6/l.

By the end of the sequential combined treatment, 89% of patients had achieved a CR, but more importantly, 11 patients among the 13 in PR after FMR could achieve a CR after treatment with ^{90}Y-IT, with a molecular negativity in 21 out of 26 assessable patients. ^{90}Y-IT is therefore an important inducer of molecular remission after conventional chemoimmunotherapy and it can improve the quality of the clinical response by converting PR to CR [24, 29], with generally mild and transient toxic effects. Regarding the hematologic toxicity, there were no differences in terms of grade 3–4 neutropenia and thrombocytopenia induced by Zevalin after a fludarabine-containing regimen in comparison with those observed after CHOP regimen and Zevalin [16].

If we compare the present results with our previous findings of phase II "FLUMIZ" study [13], we note that the conversion rate from PR to CR rate (86% in "FLUMIZ" versus 85% in this study, $P = 0.98$) and the molecular response (78% versus 81%, $P = 0.93$) are the same. The CR rate and the ORR presently observed after induction were comparable to "FLUMIZ" ones: 69% versus 71% ($P = 0.94$) and 96% versus 98% ($P = 0.94$). Similarly, the 3-year PFS was not significantly different (77% versus 81%, $P = 0.81$). Although there is a theoretical concern that rituximab may block potential binding sites for radiolabeled monoclonal antibodies, this study has shown the same percentage of conversion rate from PR to CR after ^{90}Y-IT.

These data confirm the pivotal role played by radioimmunotherapy as consolidation treatment after an induction phase: CR and PFS rates turned out to be superior if compared with those obtained by conventional chemoimmunotherapy front-line treatments, such as R-CVP

Table 3. First-line consolidation treatment with ^{90}Y-ibritumomab tiuxetan

Reference	Treatment	Pts N°	CR after induction (%)	CR after ^{90}Y-IT (%)	PFS
Jacobs et al. [16]	3xR-CHOP → ^{90}Y-IT → 4xR	60	46	89	78% at 2 years
Hainsworth et al. [17]	4xR → 3xR-CHOP or R-CVP → ^{90}Y-IT	41	30	72	64% at 5 years
Zinzani et al. [13]	6xFM → ^{90}Y-IT	61	70	96	76% at 3 years
Morschhauser et al. [15]	Various → ^{90}Y-IT	208	51	87	Median 36.5 months
McLaughlin et al. [18]	4xR-FND → ^{90}Y-IT → R-maintenance	35	69	89	74% at 3 years
This study	4xFNR → ^{90}Y-IT	55	69	89	80% at 3 years

R, rituximab; ^{90}Y-IT, ^{90}Y-ibritumomab tiuxetan.

[4] and R-CHOP [5]. Chemoimmunotherapy with following-on radioimmunotherapy has also demonstrated a higher efficacy, in terms of final CR and PFS rate, in comparison with radioimmunotherapy only (^{131}I-tositumomab) as initial treatment [30].

This study, along with other published data [15–18], suggests that radioimmunotherapy consolidation could be an important treatment approach for patients with follicular NHL.

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disclosure

The authors declare no conflicts of interest.

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