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Safety and efficacy of ^{90}Yttrium-Ibritumomab-Tiuxetan for untreated follicular lymphoma patients. An Italian cooperative study

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Summary

^{90}Yttrium (^{90}Y)-Ibritumomab-Tiuxetan combines the targeting advantage of a monoclonal antibody with the radiosensitivity of Follicular Lymphoma (FL). Previous studies showed that 90Y-IT is safe and effective in relapsed/refractory indolent FL, irrespective of prior treatment with rituximab. This multicentre trial aimed to evaluate the safety and the efficacy of "upfront" single-agent (^{90}Y)-Ibritumomab-Tiuxetan in advanced-stage FL. The primary objective was the incidence of responses in terms of complete (CR) and partial remission (PR). Fifty patients with stage II "bulky", III or IV FL received a single treatment course with (^{90}Y)-Ibritumomab-Tiuxetan as initial therapy. The median age was 60 years. Bone marrow involvement (<25%) was observed in 24 patients (48%) and 7 (14%) had an elevated lactate dehydrogenase level. The overall response (ORR) and CR rates were 94% and 86%, respectively with a median follow-up of 38·8 months. The median progression-free survival (PFS) was not reached, whereas the 3-year estimated PFS and overall survival (OS) rate was 63·4% and 90%, respectively. Grade 3/4 neutropenia and thrombocytopenia occurred in 30% and 26% of patients respectively; none experienced grade 3/4 non-haematological toxicity. No cases of secondary haematological malignancies were observed. (^{90}Y)-Ibritumomab-Tiuxetan was demonstrated to be highly effective and safe as first-line treatment for advanced-stage FL.

Keywords: follicular lymphoma, (^{90}Y)-Ibritumomab-Tiuxetan, high complete remission rate.

Approximately 90% of patients with follicular lymphoma (FL) present with disseminated disease, which is considered incurable with standard treatments (Jones *et al*, 1983). The treatment paradigm for advanced-stage FL has changed with the introduction of the anti-CD20 monoclonal antibody (MoAb), rituximab (Czuczman *et al*, 1999). MoAbs labelled with radionuclides can potentially deliver cytocidal doses of radiation to all the involved lymphoma localizations, so that radio immunotherapy (RIT) has emerged as a novel promising new therapy. Ibritumomab is a murine monoclonal immunoglobulin G1kappa antibody directed against CD20, a surface antigen that is expressed on 90% of B-cell lymphomas (Anderson *et al*, 1984), and is conjugated to the metal chelator tiuxetan for the retention of the beta emitter ^{90}Yttrium (^{90}Y). The chelation of the ^{90}Y radionuclide results in a selected delivery of cytotoxic radiation to the CD20^{+} and the surrounding microenvironment, causing tumour necrosis. Being a pure beta-emitter, ^{90}Y offers some clinical advantages over the alternative radionuclide iodine-131 (^{131}I) and it may be used in an outpatient setting (Illidge & Morschhauser, 2011).

In the initial phase I-II trial of (^{90}Y)-Ibritumomab-Tiuxetan (^{90}Y-IT), clinical responses were seen in 28 (82%) of the 34 patients with pretreated indolent non-Hodgkin lymphoma (Witzig *et al*, 1999). When ^{90}Y-IT was compared in a randomized study of relapsed or refractory FL patients to standard-dose rituximab, a significantly higher overall response rate (ORR) and complete remission (CR) rate (Witzig *et al*, 2002) was demonstrated.

Furthermore, ^{90}Y-IT has been successfully used as consolidation after first-line chemotherapy ± rituximab: the outcome was significantly improved in the advanced-stage FL

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patients compared with the observation arm in the First-Line Indolent Trial trial (Morschhauser *et al*, 2013).

Due to these encouraging results, we started a prospective cooperative pilot study, aiming to evaluate ^{90}Y-IT therapy as standard initial treatment for advanced-stage FL, irrespective of Groupe d'Etude des Lymphomes Folliculaire (GELF) criteria (Ghielmini *et al*, 2013) for treatment.

Patients and methods

Patients eligibility

Previously untreated adults (age >18 years) with stage II bulky (node >5 cm), III or IV, CD20$^+$, grade 1 or 2, FL were eligible for this trial if they had a World Health Organization (WHO) performance status (Oken *et al*, 1982) of zero to two. Patients with inadequate bone marrow function (absolute neutrophil count $\leq 1{\cdot}5 \times 10^9$/l, haemoglobin $\leq$90 g/l, platelet count $\leq 100 \times 10^9$/l) or more than 25% bone marrow involvement on trephine biopsy were excluded from the study. 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.

Baseline studies

All patients enrolled in this trial were required to undergo a full history, physical examination, complete blood cell count with differential leucocyte count, platelet count, computed tomography (CT) scan of the neck, chest, abdomen and pelvis, bone marrow aspiration and biopsy. As good medical practice, patients were also tested for blood chemistry (including creatinine clearance, liver function tests, uric acid, and lactate dehydrogenase). All cases were scored according to the Follicular Lymphoma International Prognostic Index (FLIPI) (Solal-Céligny *et al*, 2004).

Molecular analysis methods

Real-time qualitative and quantitative polymerase chain reaction (RQ-PCR) evaluation of *BCL2/IGH* rearrangement for minimal residual disease (MRD) was performed at baseline, week 14, months 6, 12, 18 and 24 and yearly thereafter where possible. DNA was extracted at the same time both from peripheral blood (PB) and bone marrow (BM) mononuclear cells using the Wizard Genomic DNA purification kit (Promega, Madison, WI, USA). In order to amplify *BCL2/IGH* rearrangement, qualitative nested PCR reactions were performed in a final volume of 25 μl using 1 μg of DNA. The first round of PCR was performed for 25 cycles and the second one for 30 cycles; primers for detection of the major breakpoint region (MBR) and reaction conditions were as previously described (Gribben *et al*, 1991). A second multiplex reaction was performed to detect the *BCL2/IGH* minor cluster region by using a JH consensus primer and three different oligonucleotides, according the BIOMED-2 standardization protocols (van Dongen *et al*, 2003). The RT-PCR was performed using a TaqMan assay and a standard curve obtained by serial dilution of genomic DNA purified from DOHH2 BCL2-MBR positive cell line. Data were analysed using the international guidelines for interpretation of real-time quantitative PCR data (van der Velden *et al*, 2007). All tests were centralized and performed in a single laboratory (Haematology Unit, Pisa University, Pisa, Italy).

Patients were identified as PCR-positive when both qualitative and quantitative PCR for the *BCL2/IGH* rearrangement were positive. When discordant results were observed between PB and BM, patients were considered to be positive when at least one sample was positive (Léonard *et al*, 1998).

Treatment plan

All patients received the ^{90}Y-IT standard regimen as follows: a first rituximab 250 mg/m^2 infusion was given alone on day 1. A second infusion of rituximab, administered 1 week later, on day 8 ($\pm$1), was followed immediately by 15 MBq/kg of ^{90}Y-IT, given as a slow intravenous push over 10 min. A maximum dose of 1200 MBq ^{90}Y-IT was administered to those patients whose body weight exceeded 80 kg. ^{90}Y-IT was routinely administered on an outpatient basis in view of the lack of gamma emissions. Disease status was evaluated using physical examination, bone marrow biopsy, a CT scan of the neck, chest, abdomen and pelvis, as well as other clinically relevant information from 28 d before and up to 98 d after ^{90}Y-IT administration. This assessment was repeated at months 6 and 12, and yearly thereafter after ^{90}Y-IT infusion. Safety and tolerability were assessed by monitoring the incidence, severity and type of any adverse event. Adverse events were graded according to the Common Toxicity Criteria version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Responses were classified according to the International Workshop Response Criteria (Cheson *et al*, 1999).

Patient follow-up

Those patients who achieved an objective response after completion of treatment and re-staging were followed without further treatment. Patients were examined with a complete re-staging at 6-month intervals. Re-staging included physical examination, complete blood counts, chemistry profile, repeated CT scanning of the chest and abdomen and any other specific studies required to reassess areas of known lymphoma involvement. At the time of lymphoma progression, patients were removed from study and further treatment (as well as the decision regarding the need for additional biopsy) was at the discretion of the treating physician.

Statistical methods

This non-randomized phase-II trial was conducted in order to evaluate the feasibility, toxicity and efficacy of the novel ^{90}Y-IT treatment regimen. All patients were included in the evaluation of toxicity. Treatment-related toxicities were graded using the National Cancer Institute Common Toxicity Criteria, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). The primary efficacy endpoint was the clinical CR rate. The secondary objectives were safety and tolerability of a single dose of ^{90}Y-IT by monitoring haematology and biochemistry parameters as well as adverse events and progression-free survival (PFS), measured from the first day of treatment to the date of documented lymphoma progression, relapse or death from any cause. Overall survival (OS) was measured from the first day of treatment until the date of death. Actuarial survival curves were constructed using the Kaplan–Meier method Kaplan and Meier (1958). GELF criteria were retrospectively evaluated in our study population to separate patients with low tumour burden (LTB) and high tumour burden (HTB). The univariate and multivariate analysis model of patients outcome included sex, age (≤60 vs. >60 years), histology type (grade 1 vs. grade 2 FL), bone marrow involvement (presence vs. absence), B symptoms (presence vs. absence), clinical stage (IV vs. other), serum lactate dehydrogenase (normal vs. elevated), FLIPI risk scores (0–2 vs. 3–5 factors), GELFcriteria for disease requiring treatment (presence vs. absence) (Ghielmini *et al*, 2013). B symptoms were not included as a variable in the multivariate analysis because it occurred in 2 patients only.

Results

Patient characteristics

Between January 2007 and December 2010, 50 patients were enrolled in this multicentre phase-II trial. Patient characteristics are listed in Table I. The median age was 60 years (IQR 25% 50 years; 50% 60 years; 75% 67 years); all patients had good performance status. All patients had low histological grade I-II. Twenty-four patients (47%) had bone marrow involvement and high-risk FLIPI (≥3) was present in 17 patients (34%). One patient only had stage II bulky at diagnosis, 21 patients had stage III (42%), and 28 patients stage IV (56%). Serum lactate dehydrogenase was elevated in 7 patients (14%). Median follow-up from diagnosis was 43·9 months. Median time from diagnosis to treatment was 3 months (IQR 25% 1·9 months; 50% 2·7 months; 75% 3·6 months).

Table I. Characteristics of the 50 patients with advanced stage follicular lymphoma.

Characteristic	Number of patients
Age (range 37–81 years)	
≤60 years	25
>60 years	25
Sex	
Male	24
Female	26
Stage of follicular lymphoma at study entry	
II bulky	1
III	21
IV	28
Histological classification	
Grade 1 follicular centre-cell lymphoma	20
Grade 2 follicular centre-cell lymphoma	30
Bone marrow involvement	
None	26
1% to 25%	24
Serum lactate dehydrogenase	
Normal	43
Elevated (>1 × normal)	7
FLIPI score	
0–1	7
2	26
≥3	17
GELF criteria for active disease	
Present	19
Absent	29
Unknown	2
Polymerase chain reaction status	
BCL2/IGH-positive	31
BCL2/IGH-negative	16
Unknown	3

FLIPI, follicular lymphoma international prognostic index; GELF, Groupe d'Etude des Lymphomes Folliculaire.

Efficacy

All 50 patients completed treatment with rituximab plus ^{90}Y-IT and all patients were evaluable for response. Forty-seven patients (94%) had an objective response, with 43 patients (86%) achieving CR. One patient had disease progression at the 6-month CT evaluation and 2 patients died while in CR. Twenty out of 24 patients with pre-treatment bone marrow involvement achieved renormalization of bone marrow after 6 months from completion of therapy. Three out of the 4 patients who obtained a partial response (PR) did not require further treatments during the observation period.

Of the 47 patients who achieved CR or PR, relapse or progression occurred in 16 patients (34%) without any sign of histological transformation, whereas 5 patients (10·6%) died of disease progression.

After a median follow-up of 38·8 months from treatment, the median PFS and OS for the whole population was not reached (Fig. 1A, B). The estimated 3-year PFS and OS by the Kaplan–Meier method was 63% and 90%, respectively.

Clinical outcomes according to GELF criteria were evaluated retrospectively and the data were fully available for 48 out of 50 patients enrolled (Ghielmini *et al*, 2013). The median PFS and OS for the 19 patients (40%) who fulfilled GELF

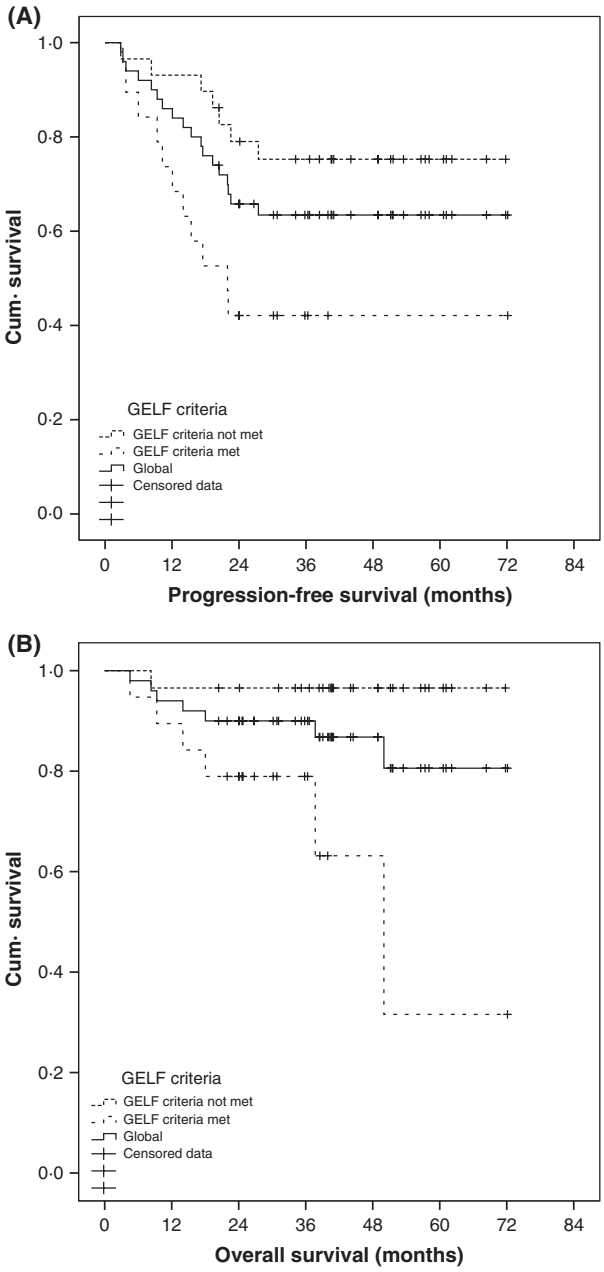

Fig 1. (A) Progression-Free Survival and (B) Overall Survival in 50 patients with advanced stage follicular lymphoma treated with ^{90}Y-Ibritumomab-Tiuxetan. GELF, Groupe d'Etude des Lymphomes Folliculaire.

criteria was 21·9 months (95% confidence interval [CI] 12·5–31·3 months) and 50 months (95% CI 31·8–68·1 months) respectively, whereas these had not been reached in the remaining 29 patients. The estimated 3-year OS and PFS in patients with LTB were 97% and 75%, respectively.

When potential predictors for response were analysed by forward/backward model selection, only GELF criteria was strongly associated with a higher risk of disease progression, as well as a poorer survival in both univariate (P = 0·009 and P = 0·002 for PFS and OS) and multivariate analyses (P = 0·007 and P = 0·011 for PFS and OS), suggesting that tumour burden might be an independent risk factor for response after ^{90}Y-IT (Table II). Univariate analysis indicated that worse OS was associated with FLIPI (P = 0·039) and age (P = 0·008), but they were not significant in the multivariate analysis. None of the remaining factors analysed had an impact on PFS and OS.

Molecular analysis results

Among the 50 patients enrolled in the study, 47 patients were also evaluated for molecular analysis on both PB and BM. Results were concordant in 72% of cases, and the *BCL2/IGH* rearrangement was detected at diagnosis in 31 patients (66%). These 31 patients were considered in the MRD analysis.

The positive PCR status at diagnosis did not correlate with any clinical feature (age, sex, stage, systemic symptoms, FLIPI score, histological grading). The median value of *BCL2/IGH* copies at diagnosis was 2342 (range 10–31980).

By 6 months of follow-up, 30 out of 31 patients had been evaluated for *BCL2/IGH* rearrangement and 23 (77%) of them had become *BCL2/IGH* negative. With a median molecular follow-up of 18 months (range 4–49), a further 4 patients achieved PCR negativity and another 4 patients became *BCL2/IGH* positive again. At the last molecular evaluation, 23 patients were PCR negative with a mean value of *BCL2/IGH* copies of 4·6 (0–110).

Whereas the molecular status assessed at 3 and 6 months did not predict relapse, MRD-negativity after 6 months from treatment showed a significant favourable prognostic value on PFS: the 30-month PFS was 80% for *BCL2/IGH*-negative vs. 46% for *BCL2/IGH* positive patients (P = 0·0039).

Safety

Grade 3/4 toxicity was limited to myelosuppression only and is detailed in Table III. Grade 3/4 neutropenia and/or thrombocytopenia occurred in 30% and 26% of patients, respectively. In these patients, the median neutrophil and platelet nadir occurred on day +36 (range +11; +41) and day + 35 (range +27; +38) from ^{90}Y-IT infusion, respectively. The lowest median neutrophil and platelet values were $0·7 \times 10^9$/l (range, $0·16–0·98 \times 10^9$/l) and 29×10^9/l (range, 13–44×10^9/l), respectively. However, there were no episodes of neutropenic fever or bleeding. All patients with grade 4 neutropenia received myeloid growth factors. Two patients required a single platelet transfusion, whereas no red blood cell transfusions were necessary. By week 14, grade 3/4 myelosuppression had improved to grade ≤1 in all patients. Two patients died in CR, one of spontaneous intra-cerebral haemorrhage with normal platelet count and one of pulmonary embolism at 10 and 14 months after RIT, respectively. Both deaths were not considered as related to therapy due to the

Table II. Prognostic factors: univariate and multivariate analyses.

	Univariate analysis PFS (months)				
Factor	Mean	Median	*P*	Multivariate analysis HR	*P*
Sex					
Female	49·3	N/R	0·825	1·027	0·954
Male	50·1	N/R			
Age					
<60 years	56·4	N/R	0·196	2·022	0·308
>60 years	40·1	N/R			
Stage					
II or III	52·2	N/R	0·736	1·608	0·677
IV	49·9	N/R			
LDH					
Normal	53·3	N/R	0·116	2·105	0·394
High	23·0	21·9			
FLIPI					
Low/intermediate	55·1	N/R	0·143	2·050	0·288
High	40·8	N/R			
GELF criteria					
Not met	58·2	N/R	0·009	5·611	0·020
Met	37·5	21·9			
Bone marrow					
Not infiltrated	49·3	N/R	0·626	2·905	0·379
Infiltrated	52·6	N/R			

PFS, progression-free survival; HR, hazard ratio; LDH, lactate dehydrogenase; FLIPI, follicular lymphoma international prognostic index; GELF, Groupe d'Etude des Lymphomes Folliculaire.

Table III. Grade 3 to 4 haematological toxicity in 50 patients with advanced stage follicular lymphoma.

	Absolute neutrophil count (range)	Platelet count (range)
Grade 3 or 4	30%	26%
Grade 4	6%	10%
Median nadir value ($\times 10^9$/l)	0·70 (0·16–0·98)	29 (13–44)
Median time to nadir (days)	36 (11–41)	35 (27–38)

long period from ^{90}Y-IT infusion. Secondary solid neoplasms were diagnosed in 4 patients (two prostate cancer at 16 and 32 months, one renal cell carcinoma at 18 months and one transitional cell carcinoma of bladder at 29 months after ^{90}Y-IT infusion). Importantly, no cases of myelodysplastic syndrome (MDS) or acute leukaemia were recorded.

Discussion

This study aimed to evaluate the efficacy and safety of a single-dose ^{90}Y-IT as first line treatment in patients with FL. The treatment was well tolerated, with reversible and manageable haematological toxicity grades >2 as the only adverse events. No cases of MDS or acute myeloid leukaemia were observed during a median follow-up of 38·8 months. This suggests that ^{90}Y-IT is safe and feasible as a first-line therapy, even in the elderly population. Overall, we found that a single course of ^{90}Y-IT resulted in an impressive remission rate (94% ORR, 86% CR). To this end, it has to be pointed out that about two-thirds of the patients did not fufil the GELF criteria for treatment, indicating the presence of an indolent disease. The use of RIT in an untreated FL population was first explored by Kaminski *et al* (2005). They reported the results of 76 patients treated with a single-dose ^{131}I-tositumomab, achieving an ORR of 95% and a CR rate of 75%. Recently, the study has been updated and remarkably, 40% of patients remain in CR at 10 years (Kaminski *et al*, 2011).

Our results are basically in line with those obtained with ^{131}I-tositumomab in untreated FL patients with advanced disease in terms of both clinical efficacy and safety profile. Differences in patient's characteristics at the baseline prevents a solid comparison between the two RIT approaches, although in our study there was a significantly higher proportion of patients older than 60 years.

Although it is widely accepted that untreated patients with FL fulfilling the GELF criteria must be treated, it still remains an open question whether or not the so-called "watch and wait" population with LTB deserves first-line therapy in the rituximab era (Kahl, 2012).

The British Intergroup Trial compared the "watch and wait" approach with the up-front treatment with rituximab as single-agent (*Ardeshna et al, 2010*). The ORR at 7 months was 6% in Arm A (watch and wait) vs. 74% in Arm B

(Rituximab induction) and 88% in Arm C (induction + maintenance), with the highest CR rate of 76% in Arm C. The proportion of patients who were progression-free at 3 years was 33% in Arm A, 58% in Arm B and 81% in Arm C.

Rituximab monotherapy induction as first-line therapy in LTB patients was also adopted in the Rituximab Extended Schedule or Retreatment Trial (RESORT), which compared rituximab maintenance versus re-treatment upon disease progression in responders to induction (Kahl *et al*, 2011). They found an ORR of 71% following 4 weekly doses of induction rituximab and no significant difference in terms of clinical benefit between the 2 comparison arms. These results clearly indicate that initial treatment with rituximab can provide a low-risk treatment strategy that could delay the need for new therapies in untreated LTB FL.

Compared to single agent rituximab, our data also seem to support the finding that the use of ^{90}Y-IT in this setting can obtain an higher rate of CR when, whereas speculations on clinical benefit would require more patients and longer follow-up.

The efficacy and toxicity of fractionated ^{90}Y-IT as an initial therapy of FL with HTB has been recently characterized by remarkable results (Illidge *et al*, 2011). In this study, patients with >20% BM involvement required rituximab pre-treatment and proceeded to RIT only if a repeat bone marrow biopsy demonstrated a ≤20% lymphoma involvement. With a median follow-up of 1·52 years, the PFS was 67% and 10 patients experienced at least one severe adverse event.

More recently, Scholz *et al* (2013) published the results of a multicentre European phase II trial of single-dose ^{90}Y-IT on 59 untreated patients with FL requiring therapy. The ORR at 6 months was 87% (with a 56% CR or undefined CR rate and a 31% PR rate, whereas the median PFS was 25·9 months. Results in our 19 patients with HTB do not differ significantly from the study reported by Scholz *et al* (2013); however, none of the predictive factors analysed, except the GELF criteria, correlated with clinical outcomes, a fact that may account for the different selection criteria for treatment in our study.

On the basis of our data and evidence from literature, the role of RIT in FL patients with HTB as first-line therapy remains largely undefined, given the excellent results of rituximab combined with chemotherapy. Nevertheless, it may be argued that, for FL patients requiring treatment who refuse chemotherapy or who are not suitable candidates, RIT as single agent should be considered as a relatively non-toxic alternative strategy, with an ORR rate above 90%.

With regard to the safety of our treatment schedule, grade 3–4 adverse events were solely limited to haematological abnormalities, but no episodes of neutropenic fever or bleeding were documented. Moreover, the occurrence of second malignancies, which were diagnosed in 4 patients, was unlikely to be related to ^{90}Y-IT considering the median age of our patient cohort and the much longer latency of radiation-induced neoplasms.

In conclusion, the feasibility of a single 1-week treatment with ^{90}Y-IT regimen demonstrated in our trial, supports the theoretical role for single agent RIT in the treatment paradigm of advanced stage FL. The RIT approach might be particularly desirable to delay more intensive strategies including chemotherapy or radiation, mainly in elderly patients with co-morbidities, regardless of tumour burden. Long-term follow-up still remains a major limitation for clinical trials in untreated FL to assess OS benefit and unexpected late effects.

Author's contributions

Nati S, Vitolo U, Botto B, Ciochetto C, Petrini M, Galimberti S, Ciabatti E, Orciuolo E, Zinzani PL, Cascavilla N, Guolo F, Fraternali G, Carella AM performed the research; Pica GM, Ibatici A analysed the data and wrote the paper, Carella AM designed the research study and reviewed the paper.

Conflict of interest

The authors do not have any competing interests.

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