ORIGINAL ARTICLE

PHASE II TRIAL OF SHORT-COURSE R-CHOP FOLLOWED BY $^{90}$Y-IBRITUMOMAB TIUXETAN IN PREVIOUSLY UNTREATED HIGH-RISK ELDERLY DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS.

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Running title: Short-course R-CHOP + $^{90}$Y-ibritumomab tiuxetan in DLBCL.

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ABSTRACT

Purpose: To evaluate the efficacy and safety of the treatment with $^{90}$Y-ibritumomab tiuxetan following a short-course of rituximab-CHOP (R-CHOP) in high-risk elderly patients with previously untreated diffuse large B-cell lymphoma (DLBCL).

Experimental design: From December 2006 to October 2008, 55 high-risk elderly (age ≥ 60 years) untreated DLBCL patients were treated in seven Italian Institutions with a short-course of chemotherapy consisting of 4 cycles of R-CHOP followed by $^{90}$Y-ibritumomab tiuxetan 6 to 10 weeks later.

Results: Forty-eight out of 55 patients underwent to radioimmunotherapy. The overall response rate to the entire treatment regimen was 80%, including a 73% of complete remissions and a 7% of partial remissions. Eight (50%) of the 16 patients who achieved less than a CR with CHOP could improve their remission status after $^{90}$Y-ibritumomab tiuxetan administration. With a median follow-up of 18 months, the 2-year progression-free survival was estimated to be 85%, with a 2-year overall survival (OS) of 86%. $^{90}$Y-ibritumomab tiuxetan toxicity consisted of grade 3-4 hematologic toxicity in 28/48 patients, mainly neutropenia (23 patients) and thrombocytopenia (15 patients). Red cells and/or platelets transfusions were given to 3 patients.

Conclusion: This study has evaluated the feasibility, efficacy and safety of a short-course R-CHOP regimen followed by $^{90}$Y-ibritumomab tiuxetan in high-risk elderly DLBCL patients.
STATEMENT OF TRANSLATIONAL RELEVANCE

In the subset of elderly diffuse large B-cell lymphoma (DLBCL), the concept of a sequential treatment with different targeted drugs and mechanisms and, at the same time, the reduction of conventional chemotherapy with its hematologic and extra-hematologic side effects, could represent the best therapeutic armamentarium in order to try to cure the majority of these patients. In this case, the roles of chemotherapy, immunotherapy and radioimmunotherapy as single approaches are well defined and absolutely positive. In this histological subset, it is very important to increase the rate of complete responses after induction and consolidation phases without any cumulative toxicity.
INTRODUCTION

Several studies have reported a significant advantage in adding rituximab to CHOP in elderly patients with a newly diagnosed diffuse large B-cell lymphoma (DLBCL), and in young patients with favorable prognostic profile (1-3). Although the combination of Rituximab with CHOP (R-CHOP) as standard regimen has led to improved outcomes, there is a group of poor-risk patients which has a lower chance to be cured with standard R-CHOP, thus needing an alternative treatment strategy.

Two large randomized studies have clearly shown that the addition of Rituximab to CHOP given every 21 or 14 days has significantly improved the outcome in elderly patients (more than 60 years) compared to CHOP or CHOEP (i.e. with the addition of etoposide) but without rituximab. In the former GELA (Group d’Etude des Lymphomes de l’Adulte) study, patients were randomized to receive 8 courses of CHOP with or without rituximab every 21 days (1, 4). R-CHOP21 significantly increased the complete response (CR) rate (76% vs 63%) and reduced the risk of treatment failure and death. The superiority of overall survival (OS) rate of R-CHOP was confirmed in both low- and high-risk age-adjusted International Prognostic Index (aaIPI) groups. However, the 5-years OS rate in high-risk patients did not exceed 50% even in patients treated with R-CHOP (48% vs 39%, comparing R-CHOP and CHOP). Similarly, the 5-years event-free survival (EFS) in high-risk patients was 41% vs 27%, again comparing R-CHOP and CHOP. In the latter study (Ricover 60), conducted by the German High Grade Non Hodgkin’s Lymphoma Study Group (Deutsche Studiengruppe Hochmaligne Non-Hodgkin-Lymphome, DSHNHL), 1222 patients were randomized to receive six or eight courses of CHOP14 with or without rituximab and radiotherapy to sites of initial bulky disease (2). R-CHOP14 significantly improved 3-years EFS (66% vs 47%), progression-free survival (PFS), and OS if compared to six cycles of CHOP14 treatment.

A formal demonstration of whether R-CHOP14 is superior or not to R-CHOP21 is however still lacking. Randomized clinical trials between R-CHOP21 and R-CHOP14 are ongoing by GELA and British National Lymphoma Investigation (BNLI). The BNLI has recently reported some preliminary results on a phase III randomized trial comparing the two different schedules (462 patients in the R-CHOP21 arm and 481 in R-CHOP14): the radiological complete responses were 63% and 58% for each arm (5). Therefore, the choice between R-CHOP21 and R-CHOP14, both considered as a standard therapy,
should be based mainly on the experience of the center, on patients' performance status and co-morbidities, thus propending for a less aggressive treatment (R-CHOP21) in elderly and more clinically involved patients. In order to improve the efficacy of R-CHOP14 in elderly patients, the DSHNHL has explored a "dense" R-CHOP14 with an increased dose of rituximab. At present, the optimal dose of rituximab has not yet been established: rituximab serum levels build up slowly after infusion, and it might be possible that a dose-dense immunotherapy could be able to improve the efficacy of the treatment. The aim of the "DENSE-R-CHOP14" trial was to explore a supplemented dose intense rituximab during the first 2 cycles of R-CHOP14 in elderly patients, maintaining a single dose in the subsequent cycles, for a total of 12 doses of rituximab delivered in 6 courses of chemotherapy. Rituximab serum levels resulted markedly increased, thus suggesting a higher efficacy in poor-risk patients, with a 1-yr EFS of 74%, against 65% related to the standard R-CHOP14 treatment. On the other hand, an increased incidence of infection was also documented, mainly interstitial pneumonia (6). This strategy is currently under investigation in a controlled randomized study.

An innovative therapeutic option that should be investigated in order to increase patients’ outcomes in poor prognosis DLBCL might be the addition of radioimmunotherapy. The efficacy of the radioimmunoconjugate $^{90}$Y-ibritumomab tiuxetan has been demonstrated in patients with relapsed or refractory aggressive DLBCL, with promising response rates and durable response (7-9). Preliminary data from phase II studies in aggressive lymphomas (DLBCL and mantle cell lymphoma) suggest that $^{90}$Y-ibritumomab tiuxetan is effective also in this disease setting, namely as consolidation treatment after chemotherapy or chemoimmunotherapy (10-12).

Moving from these data and from our previous experience on the role of $^{90}$Y-ibritumomab tiuxetan after CHOP in untreated high risk elderly DLBCL patients (11), we have designed a phase II trial aimed at increasing the global treatment efficacy including $^{90}$Y-ibritumomab tiuxetan, along with a decreased exposure to cytotoxic drugs by using a short-course R-CHOP chemotherapy. In this trial, patients were to receive R-CHOP21 for 4 cycles, instead of 6 cycles, followed by treatment with $^{90}$Y-ibritumomab tiuxetan.
PATIENTS AND METHODS

Patients’ eligibility and demography

Patients older than 65 years of age (or aged 60 to 65, but not eligible for high-dose therapy with autologous stem cell transplantation) with biopsy-proven and bidimensionally measurable stage II (with bulky disease), stage III, or stage IV DLBCL, expressing the CD20 antigen, were eligible for this trial. Patients were to be previously untreated, with a WHO performance status ≤ 2 and a high-intermediate or high aa-IPI score (13).

Fifty-five patients have met inclusion criteria and have subsequently been enrolled in this trial amongst 7 Italian cooperative institutions; enrolment started in December 2006 and was concluded in October 2008, when the study reached its completion and was closed.

Patients’ characteristics are listed in Table 1. The median age of patients on the trial was 70 years, with a range of 61 to 83 years. Twenty-six (47%) were male and 29 (53%) were female. Four patients were stage II (with bulky disease), 51 stage III-IV. Eight patients (14.5%) had bulky disease.

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 has been approved by the institutional review board, and has been registered at ClinicalTrials.gov §, NCT00850512.

All diagnostic biopsies were reviewed by an expert pathologist (S.P.) from our Institute, and then categorized in accordance with the WHO classification (14).

Baseline studies

All the patients enrolled into this trial were required to undergo a full history, physical examination, complete blood cell count with leukocyte differential, platelet count, computed tomography (CT) scan of neck, chest, abdomen and pelvis (with and without contrast), 18F-fluorodeoxyglucose (FDG)-PET scan and bone marrow aspiration and biopsy. Bulky disease was defined as the presence of a nodal or extranodal mass equal to or greater than 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, §

http://www.clinicaltrials.gov
and hepatitis-C virus antibodies), uric acid, lactate dehydrogenase, HIV, and underwent to urinalysis and electrocardiography. Patients with a history of impaired cardiac status were furtherly evaluated by echocardiography, and were then considered eligible if the cardiac ejection fraction was within normal ranges.

**Treatment plan**

Patients were treated by R-CHOP21 chemotherapy every 21 days for 4 cycles; standard doses of 375 mg/m² rituximab, 750 mg/m² cyclophosphamide, 50 mg/m² doxorubicin, and 1.4 mg/m² (maximum total dose of 2.0 mg) vincristine were administered intravenously on day 1; 100 mg/day prednisone was given orally for 5 days for each cycle, starting from day 1. Oral allopurinol (300 mg/day) was recommended for at least 15 days as an adjunctive therapy for patients with bulky disease.

If there had been fewer than 1,500/μL granulocytes or fewer than 100,000/μL platelets by the time the next cycle was due, treatment should have been delayed for 1 week and blood counts then repeated. If blood counts had not recovered after 2 weeks, the patient should have been treated at the 75% of the last dose of cyclophosphamide and doxorubicine received. A subsequent dose re-escalation could have been taken into consideration at the discretion of the treating physician.

Granulocyte colony-stimulation factor (G-CSF) was not administered in order to prevent neutropenia, according to our institution guidelines; patients who experienced grade 3 or 4 neutropenia or developed neutropenic fever between cycles of chemotherapy were allowed to receive growth factors, at the discretion of the treating physician.

**Restaging**

Patients were restaged 3 to 4 weeks after the completion of the fourth cycle of R-CHOP21 chemotherapy, through a complete physical examination, blood testing, CT scan, PET scan and bone marrow aspiration and biopsy (if bone marrow involvement was documented during baseline evaluation).

Responses were classified according to the revised response criteria for malignant lymphoma (15).

Patients achieving at least a partial response (PR) after 4 cycles of R-CHOP21 were considered eligible for further consolidation with ⁹⁰Y-ibritumomab tiuxetan, provided a granulocyte count and a platelet count greater than 1,500/μL and 100,000/μL respectively,
and a bone marrow lymphoma infiltration not exceeding the 25% of the total marrow cellularity, as assessed on completion of the induction chemotherapy.

Six to 10 weeks after completing the fourth cycle of R-CHOP21 chemotherapy, eligible patients were treated with a single course of $^{90}$Y-ibritumomab tiuxetan (Figure 1). The radioimmunotherapy treatment plan consisted of an initial infusion of rituximab, at a dose of 250 mg/m$^2$ on day 1, then repeated on days 7, 8 or 9. The second infusion of rituximab should have been immediately followed by a weight-based dose of $^{90}$Y-ibritumomab tiuxetan (Bayer Schering Pharma, Berlin, Germany), given as a slow intravenous push over 10 minutes. The dose of $^{90}$Y-ibritumomab tiuxetan was estimated in 11.1 MBq/kg (0.3 mCi/kg) for patients with a pre-treatment platelet count of 100,000-149,000/µL and 14.8 MBq/kg (0.4 mCi/kg) for those with a platelet count of at least 150,000/µL. In all cases, the maximum total dose was 1184 MBq (32 mCi). $^{90}$Y-ibritumomab tiuxetan was routinely administered on an outpatient basis in view of the lack of gamma emissions.

Because of the transitory myelosuppression generally observed after the administration of $^{90}$Y-ibritumomab tiuxetan, a complete blood cell count with leukocyte differential and platelet count was performed in all patients on a weekly basis, from the third week after radioimmunotherapy until the complete hematological recovery.

Disease status was evaluated again upon treatment completion, through physical examination, bone marrow biopsy (if still positive after induction chemotherapy), CT scan of neck, chest, abdomen and pelvis (with and without contrast), 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-hematological toxicity, have also been recorded. Patients’ re-assessment was repeated 3 months after $^{90}$Y-ibritumomab tiuxetan infusion.

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

Statistical analysis

The primary endpoint of this study was the assessment of the response rate (including PET evaluation) associated with R-CHOP21 plus radioimmunotherapy.
Sample size estimation was carried out by Fleming’s single stage procedure (16, 17). Previous experience shows that the response rate, adjusted for the response criteria as in par, has been 50%. Defining $\pi_0$ as the proportion of response below the treatment that does not warrant further investigations and $\pi_a$ as the proportion of responses beyond which a phase III trial should be carried out, we set $\pi_0 = 0.6$ and $\pi_a = 0.8$. The number of patients required, given a type I error ($\alpha$) at 0.05 two sided and a power of $1-\beta = 80\%$, is 48 and the number of successes (responses) 33. Considering a drop-out rate of about 10%, the sample size is fixed at 55. If, at the end of the trial, at least 33 responses (successes) are observed, the treatment will be accepted for a phase III trial (18).

OS and PFS curves were plotted by the Kaplan-Meier method (19). PFS was defined as the time interval from diagnosis to the first observation of disease relapse or death as a result of any cause. CR and PR rates, as well as the proportion of patients with progressive disease (PD) are expressed on an intention-to-treat basis.
RESULTS

Clinical Response

At the time of re-assessment after 4 cycles of R-CHOP21, overall response (OR) rate was 89% with 32 out of 55 (58%) patients achieving a CR and 17 out of 55 (31%) patients achieving a PR; the remaining 6 patients had progressive disease.

Forty-eight out of 55 patients (more specifically, all the patients with CR and 16 patients with PR) were deemed eligible for subsequent consolidation with $^{90}$Y-ibritumomab tiuxetan. The remaining patient with PR showed a lymphoma progression two weeks before radioimmunotherapy, and was then considered ineligible for consolidation treatment. There is no record of any patient receiving a reduced dose of $^{90}$Y-ibritumomab tiuxetan because of persisting thrombocytopenia following R-CHOP21.

The CR rate after the end of the entire treatment (all the 4 cycles of R-CHOP21 and the administration of $^{90}$Y-ibritumomab tiuxetan) was 73% (40 patients out of 55). Four patients still remained in PR and 11 showed disease progression (4 patients previously in PR and all the 7 uneligible to radioimmunotherapy).

The OR rate to the entire treatment was 80%, including 73% CR and 7% PR. The therapy with $^{90}$Y-ibritumomab tiuxetan has therefore substantially improved the CR rate (Table 2). In particular, the addition of $^{90}$Y-ibritumomab tiuxetan has improved the overall best response (from PR to CR) in 8 (50%) patients out of the 16 in PR after the only R-CHOP21 regimen.

Among the CR patients, 4 of them have experienced a disease relapse after 6, 8, 12, and 14 months, respectively.

At median follow-up time of 18 months (range, 9-25), 4 patients have experienced a disease relapse and 12 have had a lymphoma progression, yielding an estimated 2-year DFS of 85% and an estimated 2-year OS of 86% (Figure 2).

Safety

There were no treatment-related deaths. The R-CHOP21 regimen was well tolerated by most of the patients. Reversible hematologic toxicities constituted most of the adverse events, with grade 3 hematologic toxicity in 21 (39%) patients and grade 4 in seven patients (13%), mainly consisting of neutropenia. Four patients (9%) developed
febrile neutropenia, and 2 of them required hospitalization and intravenous antibiotic treatment.

Regarding $^{90}$Y-ibritumomab tiuxetan, there were no infusion-related reactions. Adverse events after $^{90}$Y-ibritumomab tiuxetan treatment were primarily hematologic and transient; no patient discontinued treatment because of an adverse event. The severity of the hematologic toxicity (expressed as the lowest – i.e. *nadir* – concentration of granulocytes, platelets and hemoglobin reached after radioimmunotherapy) and its duration are reported in Table 3. Grade 3-4 thrombocytopenia and neutropenia occurred in 19 patients (39.5%) and 23 patients (48%), respectively. Seven patients (14.5%) received granulocyte colony-stimulating factors; only 3 patients (6.2%) received platelet transfusions, and none received red blood cells transfusions.

No patients have shown a TSH elevation, nor any secondary malignancies have occurred.
DISCUSSION

This study was aimed at establishing the feasibility, tolerability, and efficacy of a sequential treatment with 4 cycles (instead of the conventional 6) of R-CHOP, delivered every 21 days, followed by the administration of $^{90}$Y-ibritumomab tiuxetan as a front-line therapy in elderly untreated DLBCL patients. Patients up to age 83 have tolerated the planned sequential treatment regimen well.

Coiffier et al (1) have demonstrated that the addition of rituximab to CHOP21 is able to improve the survival outcomes in elderly patients with DLBCL, without significant increase in toxicity, if compared to CHOP21 alone. To better define whether combining dose-dense CHOP14 with rituximab improves results in elderly patients further, 1222 patients have been enrolled in the RICOVER-60 trial, and then randomized to receive 6 or 8 cycles of CHOP14 with or without rituximab (2). The results obtained with 6 cycles of R-CHOP14 clearly indicate that this is the preferred treatment for elderly patients, to which other approaches should be compared. However, to become the worldwide standard of care for elderly patients, R-CHOP14 must be confirmed to be superior to R-CHOP21, as the ongoing GELA and MRCI trials in France and Great Britain (5, 20) are supposed to do.

Despite markedly superior outcomes in first-line treatment following the addition of rituximab to the CHOP regimen, with dose-dense/dose-intense regimens also playing a potential role (2, 3, 21-23), the prognosis for patients older than 60 still remains poor, with a 7-year OS rate of 53%, as reported in one study (21). At least 30% to 50% of these patients, with an advanced-stage DLBCL, will fail to attain a remission with primary therapy, or will experience disease relapse after achieving a remission. Occasionally, asymptomatic patients can be managed with a watch and wait approach if they are not candidates for aggressive therapy, and only selected patients may experience prolonged remissions with involved-field radiation therapy. However, the vast majority of patients will require a second-line (salvage) chemotherapy. Alternative treatment approaches should therefore be addressed at reducing the risk for disease relapse, for example by improving first-line therapeutic strategies, particularly in older patients not eligible for autotransplant.

Recently, on the basis of the “consolidation” concept experienced with $^{90}$Y-ibritumomab tiuxetan in follicular lymphomas, some reports have also pointed out the positive role of $^{90}$Y-ibritumomab tiuxetan in elderly DLBCL patients (11, 12, table 4) after a chemotherapy or chemo-immunotherapy induction. Early results have indicated that $^{90}$Y-
ibritumomab tiuxetan consolidation has a favourable tolerability profile, with low infection rates and a manageable hematologic toxicity. In addition, responses have improved after consolidation, and OS and DFS rates seem to be very encouraging. The objective of consolidation therapy is to rapidly improve the response to induction therapy, not only by converting a PR to a CR, but also by reducing the relapse risk of responders. For this reason we decided to use all the therapeutic approaches (chemotherapy, immunotherapy and radioimmunotherapy) reducing conventional chemotherapy (from 6 to 4 courses) and its related toxicity in this subset of elderly patients.

By the end of this sequential combined treatment, 40 (73%) patients had achieved a CR and 4 (7%) a PR, with an estimated 2-years PFS of 85%. More importantly, among the 16 patients who achieved a PR with R-CHOP21, 8 (50%) could improve their remission status after treatment with $^{90}$Y-ibritumomab tiuxetan. Toxic effects were generally mild and transient, without any aspect of cumulative toxicity.

Early results of the “DENSE-R-CHOP14” in elderly DLBCL patients suggest that dose-dense rituximab can improve the outcome of elderly poor-prognosis patients (24): CR rate of 81% and 1-year EFS of 74% have, in fact, been obtained.

These data are comparable to our results after only 4 R-CHOP21 courses and subsequent consolidative radioimmunotherapy, thus confirming the pivotal role of $^{90}$Y-ibritumomab tiuxetan in elderly DLBCL patients. In addition, we have wished to demonstrate the specific utility of this sequential politreatment schedule in reducing, at the same time, the global number of chemotherapy courses in such a subset of high-risk DLBCL patients.
REFERENCES


Table 1. Patients’ characteristics (n = 55).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>70 (61-83)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26 (47)</td>
</tr>
<tr>
<td>Female</td>
<td>29 (53)</td>
</tr>
<tr>
<td>Symptoms, n (%)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>39 (71)</td>
</tr>
<tr>
<td>B</td>
<td>16 (29)</td>
</tr>
<tr>
<td>Bulky disease, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (14.5)</td>
</tr>
<tr>
<td>No</td>
<td>47 (85.5)</td>
</tr>
<tr>
<td>LDH level, n (%)</td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>50 (91)</td>
</tr>
<tr>
<td>Normal</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>4 (7)</td>
</tr>
<tr>
<td>III</td>
<td>11 (20)</td>
</tr>
<tr>
<td>IV</td>
<td>40 (73)</td>
</tr>
<tr>
<td>aa-IPI score (%)</td>
<td></td>
</tr>
<tr>
<td>High-intermediate (2)</td>
<td>30 (55%)</td>
</tr>
<tr>
<td>High risk (3)</td>
<td>25 (45%)</td>
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</table>
Table 2. Response to therapy.

<table>
<thead>
<tr>
<th>Response</th>
<th>After R-CHOP21 n (%)</th>
<th>After R-CHOP21 + $^{90}$Y-ibritumomab tiuxetan n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>32 (58)</td>
<td>40 (73)</td>
</tr>
<tr>
<td>Partial response</td>
<td>17 (31)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>6 (11)</td>
<td>4 (7)</td>
</tr>
</tbody>
</table>
Table 3. Hematologic toxicity after radioimmunotherapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Nadir (range)</th>
<th>Days from Baseline to nadir</th>
<th>Median duration of grade 3-4 nadir (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC, cells/mm³</td>
<td>3500 (1550-6120)</td>
<td>700 (210-2950)</td>
<td>37 (22-59)</td>
<td>30 (12-65)</td>
</tr>
<tr>
<td>Platelets, cells/mm³</td>
<td>233 (154-498)</td>
<td>37 (10-121)</td>
<td>32 (19-38)</td>
<td>21 (9-52)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.1 (11.4-15.2)</td>
<td>11.3 (8.9-13.0)</td>
<td>41 (20-55)</td>
<td>/</td>
</tr>
</tbody>
</table>

ANC: absolute neutrophil count
Table 4. First-line consolidation treatment with $^{90}$Y-ibritumomab tiuxetan.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients’ subset</th>
<th>Treatment</th>
<th>Pts N°</th>
<th>CR after induction</th>
<th>CR after $^{90}$Y-IT</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al (10)</td>
<td>Untreated mantle cell-lymphoma</td>
<td>4xR-CHOP $\rightarrow^{90}$Y-IT</td>
<td>56</td>
<td>Not reported</td>
<td>42%</td>
<td>71% FFS at 18 months</td>
</tr>
<tr>
<td>Zinzani et al (11)</td>
<td>Untreated DLBCL, age $\geq$ 60 years</td>
<td>6xCHOP $\rightarrow^{90}$Y-IT</td>
<td>20</td>
<td>75%</td>
<td>95%</td>
<td>75% PFS at 2 years</td>
</tr>
<tr>
<td>Hamlin et al (12)</td>
<td>Untreated DLBCL, age $\geq$ 60 years</td>
<td>6xCHOP $\rightarrow^{90}$Y-IT</td>
<td>39</td>
<td>Not reported</td>
<td>Not reported</td>
<td>78% PFS at 2 years</td>
</tr>
<tr>
<td>This study</td>
<td>Untreated DLBCL, age $\geq$ 60 years</td>
<td>4xR-CHOP $\rightarrow^{90}$Y-IT</td>
<td>55</td>
<td>58%</td>
<td>73%</td>
<td>85% PFS at 2 years</td>
</tr>
</tbody>
</table>

R = rituximab; $^{90}$Y-IT = $^{90}$Y-ibritumomab tiuxetan; FFS = failure-free survival; PFS = progression-free survival
FIGURE LEGEND

**Figure 1.** Treatment algorithm with *interim* and final patients’ outcomes. CR, complete response; PR, partial response; PD, progressive disease; CT, computed tomography; PET, positron emission tomography; BMB, bone marrow biopsy.

**Figure 2.** Overall survival (dotted line) and progression-free survival (solid line) curves for the entire study population.
55 patients eligible to R-CHOP21 treatment (4 cycles)

6-10 weeks

2-3 weeks

RESTAGING
CT scan, PET scan, BMB

CR (32 pts)
PR (17 pts)

1 pt in PR out of study for rapid disease progression

60Y-ibritumomab tiuxetan

12 weeks

RESTAGING
CT scan, PET scan, BMB

PR (4 pts)
CR (40 pts)
Phase II Trial of Short-Course R-CHOP Followed by $^{90}$Y-Ibritumomab Tiuxetan in Previously Untreated High-Risk Elderly Diffuse Large B-Cell Lymphoma Patients

Pier Luigi Zinzani, Giuseppe Rossi, Silvia Franceschetti, et al.

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