(Article begins on next page)

23/04/2024 08:30

Published Ahead of Print on April 11, 2019, as doi:10.3324/haematol.2018.209932.

haematologica
Journal of The Ferrata Storti Foundation

Prolonged survival in the absence of disease-recurrence in advanced-stage follicular lymphoma following chemo-immunotherapy: 13-year update of the prospective, multicenter randomized GITMO-IIL trial

by Riccardo Bruna, Fabio Benedetti, Carola Boccomini, Caterina Patti, Anna Maria Barbui, Alessandro Pulsoni, Maurizio Musso, Anna Marina Liberati, Guido Gini, Claudia Castellino, Fausto Rossini, Fabio Ciceri, Delia Rota-Scalabrini, Caterina Stelitano, Francesco Di Raimondo, Alessandra Tucci, Liliana Devizzi, Valerio Zoli, Francesco Zallio, Franco Narni, Alessandra Dondi, Guido Parvis, Gianpietro Semenzato, Francesco Lanza, Tommasina Perrone, Francesco Angrilli, Atto Billio, Angela Gueli, Barbara Mantoan, Alessandro Rambaldi, Alessandro Massimo Gianni, Paolo Corradini, Roberto Passera, Marco Ladetto, and Corrado Tarella. Collaborative Groups: GITMO (Gruppo Italiano Tapianto Midollo Osseo) [IIL (Intergruppo Italiano Linfomi)]

Haematologica 2019 [Epub ahead of print]

Citation: Riccardo Bruna, Fabio Benedetti, Carola Boccomini, Caterina Patti, Anna Maria Barbui, Alessandro Pulsoni, Maurizio Musso, Anna Marina Liberati, Guido Gini, Claudia Castellino, Fausto Rossini, Fabio Ciceri, Delia Rota-Scalabrini, Caterina Stelitano, Francesco Di Raimondo, Alessandra Tucci, Liliana Devizzi, Valerio Zoli, Francesco Zallio, Franco Narni, Alessandra Dondi, Guido Parvis, Gianpietro Semenzato, Francesco Lanza, Tommasina Perrone, Francesco Angrilli, Atto Billio, Angela Gueli, Barbara Mantoan, Alessandro Rambaldi, Alessandro Massimo Gianni, Paolo Corradini, Roberto Passera, Marco Ladetto, and Corrado Tarella Collaborative Groups: GITMO (Gruppo Italiano Tapianto Midollo Osseo) [IL (Intergruppo Italiano Linfomi)]. Prolonged survival in the absence of disease-recurrence in advanced-stage follicular lymphoma following chemo-immunotherapy: 13-year update of the prospective, multicenter randomized GITMO-IIL trial. Haematologica. 2019; 104:xxx
doi:10.3324/haematol.2018.209932

Prolonged survival in the absence of disease-recurrence in advanced-stage follicular lymphoma following chemo-immunotherapy: 13-year update of the prospective, multicenter randomized GITMO-IIL trial

Riccardo Bruna[1], Fabio Benedetti[2], Carola Boccomini[3], Caterina Patti[4], Anna Maria Barbui[5], Alessandro Pulsoni[6], Maurizio Musso[7], Anna Marina Liberati[8], Guido Gini[9], Claudia Castellino[10], Fausto Rossini[11], Fabio Ciceri[12], Delia Rota-Scalabrini[13], Caterina Stelitano[14], Francesco Di Raimondo[15], Alessandra Tucci[16], Liliana Devizzi[17], Valerio Zoli[18], Francesco Zallio[19], Franco Narni[20], Alessandra Dondi[21], Guido Parvis[22^], Gianpietro Semenzato[23], Francesco Lanza[24°], Tommasina Perrone[25], Francesco Angrilli[26], Atto Billio[27], Angela Gueli[1], Barbara Mantoan[28], Alessandro Rambaldi[5,29], Alessandro Massimo Gianni[1], Paolo Corradini[29,30], Roberto Passera[31], Marco Ladetto [19], Corrado Tarella[* 1, 29]

[1]Onco-hematology Div., IEO, European Institute of Oncology IRCCS, Milano, Italy; [2]Hematology Univ. Div., Verona, Italy; [3]Hematology Div., Città della Salute Hosp., Torino, Italy; [4] Hematology Div, Azienda Villa Sofia-Cervello, Palermo, Italy; [5]Hematology Div., Papa Giovanni XXIII Hosp., Bergamo, Italy; [6] Department of cellular biotechnologies and hematology, Sapienza University, Rome Italy; [7]Hematology Unit, La Maddalena Hospital, Palermo, Italy; [8] SC Oncoematologia, Università degli Studi di Perugia, Italy; [9]Hematology Univ. Div., Ancona, Italy; [10]Hematology Dep., Cuneo, Italy; [11] Hematology Uni. Div., Monza, Italy; [12]hematology Unit HSR, Milano, Italy; [13]Oncologia Medica, Cancer Inst. FPO, IRCCS Candiolo, Italy; [14]Hematology Div., Reggio Calabria, Italy; [15]Hematology Univ.Div., Catania, Italy; [16]hematology Div., Brescia, Italy; [17]Oncology univ. Div., Milano, Italy; [18]Hematology Div., Roma, Italy; [19]Hematology Div., Alessandria, Italy; [20]Hematology Univ. Div., Modena, Italy; [21]Oncology Div., Modena, [22] Internal Medicine Div., S. Luigi Hosp., Orbassano, Italy, [23]Hematology Univ. Div., Padova, Italy; [24]Hematology Unit, Cremona, Italy; [25]Hematology Univ. Div., Bari, Italy; [26]Hematology Div., Pescara, Italy; [27]Hematology Div., Bolzano, Italy; [28]Hematology Univ. Div., Città della Salute Hosp., Torino, Italy; [29]University of Milan, Milan, Italy; [30]Hematology Univ. Div., Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; [31]Nuclear Med Div., Città della Salute Hosp, Torino, Italy

***Correspondence:** Corrado Tarella, Divisione Universitaria di Ematologia, Istituto Europeo di Oncologia, Via Ripamonti 435, 20141 Milano, Italy; e-mail: corrado.tarella@unimi.it.

***Present address*:**
^ Div. di Ematologia, AO Mauriziano, Torino, Italy
° Hematology and SCT Unit, Ospedale di Ravenna, Italy

Summary of paper organization:

- **Text word count: 2,983**
- **Abstract word count: 251**
- **Number of Tables: 2 (+ 1 Diagram in the Online Supplement)**
- **Number of Figures: 5**
- **Number of References: 48**

Running head:

13-year update of the R-HDS vs. CHOP-R trial in FL

Article Summary:

- The 13-year update of the randomized trial of R-HDS vs. CHOP-R in high-risk follicular lymphoma (FL) demonstrates an unprecedented improvement in overall survival (OS), in both treatment arms; complete remission (CR) was the strongest predictor of prolonged OS
- The study is the longest follow-up ever reported on FL treated upfront with chemo-immunotherapy and represents a valuable benchmark for novel treatments for FL

ABSTRACT

A prospective trial conducted in 2000-2005 showed no survival advantage for high-dose chemotherapy with rituximab and autograft (R-HDS) versus conventional chemotherapy with rituximab (CHOP-R) as first-line therapy in 134 high-risk follicular lymphoma patients aged <60 year. The study has been updated at the 13-yr median follow-up. As of February 2017, 88 (66%) patients were alive, with overall survival of 66.4% at 13 years, without a significant difference between R-HDS (64.5%) and CHOP-R (68.5%). To date, 46 patients have died, mainly because of disease progression (47.8% of all deaths), secondary malignancies (three solid tumor, nine myelodysplasia/acute leukemia, 26.1% of all deaths), and other toxicities (21.7% of all deaths). Complete remission was documented in 98 (73.1%) patients and associated with overall survival, with 13-year estimates of 77.0% and 36.8% for complete remission vs. no-complete remission, respectively. Molecular remission was documented in 39 (65%) out of 60 evaluable patients and associated with improved survival. In multivariate analysis, complete remission achievement had the strongest effect on survival ($p<0.001$), along with younger age ($p=0.002$) and female sex ($p=0.013$). Overall, 50 patients (37.3%) survived with no disease recurrence (18 CHOP-R, 32 R-HDS). This follow-up is the longest reported on follicular lymphoma treated upfront with rituximab-chemotherapy and demonstrates an unprecedented improvement in survival compared to the pre-rituximab era, regardless of the use of intensified or conventional treatment. Complete remission was the most important factor for prolonged survival and a high proportion of patients had prolonged survival in their first remission, raising the issue of curability in follicular lymphoma.

This trial was registered at www.clinicaltrials.gov as no. NCT00435955

INTRODUCTION

The current first-line treatment strategy for symptomatic and advanced follicular lymphoma (FL) is chemo-immunotherapy, with rituximab in combination with various chemotherapy regimens [1-2]. For a long-time the upfront use of intensified chemotherapy with autograft has been proposed as an effective treatment option for patients presenting with high-risk disease [3-8]. We previously conducted a prospective randomized trial of these regimens in Italy, including patients younger than 60 years who were affected by high-risk FL. The results showed no survival advantage by high-dose sequential chemotherapy with rituximab and autograft (R-HDS) compared to conventional cyclophosphamide, doxorubicin, vincristine, and prednisone supplemented with rituximab (CHOP-R) [9]. Despite the limited median follow-up of 4 years, this observation has discouraged the upfront use of intensive chemo-immunotherapy with autograft in FL, including in patients with high-risk disease presentation.

FL patients now have prolonged life expectancy, with a median survival of 10 years. This survival rate is possible because of the availability of rituximab along with improvements in the supportive care instruments [10-13]. The increase in patient survival warrants a long-term update of clinical trials to evaluate the real benefit of any treatment. For this purpose, our previous results of the randomized R-HDS vs. CHOP-R have been updated by extending the period of analysis to 2017 with a median follow-up of 13 years. The prolonged observation of this prospective cohort of patients offers the opportunity to define the following in advanced-stage, high-risk FL patients: the long-term survival following conventional vs. intensified chemotherapy with autograft, both delivered with Rituximab; the main causes of death; the main factors affecting long-term outcome; and the rate of patients with prolonged survival in the absence of disease recurrence

METHODS

Patient characteristics

Between March 2000 and May 2005, a total of 136 patients were enrolled in the multicenter randomized study, launched in Italy among centers affiliated with GITMO (Gruppo Italiano Trapianto Midollo Osseo) and/or to the Italian Lymphoma Intergroup (IIL)[9]. The institutional review boards of all the participating centers approved the study. The study was designed for the first-line treatment of patients aged 16 to 60 years with a histologically proven diagnosis of FL [14]. Patients were eligible if they had Ann Arbor stage III or IV and a high-risk prognostic presentation, according to the prognostic risk scores in use at the time the protocol was designed, i.e. the age-adjusted IPI score 2 or greater and the IIL score 3 or greater for FL [15, 16]. The CONSORT Diagram in the online supplement gives details about treatment outcome of the 136 enrolled patients. Table 1 describes the main features of the 134 evaluable patients and the main clinical features of patients who are presently alive vs. those who have died since protocol entrance.

Study design, treatment schedule and end-points

Aim of the study was to assess the superiority of an intensive chemo-immunotherapy strategy including autologous hematopoietic stem cell transplantation (auto-HSCT) compared to conventional chemo-immunotherapy. A centralized computer generated a simple randomization sequence and patients were randomly assigned either to the intensified or conventional arm.

Both conventional CHOP-R and intensified R-HDS treatments already have been described [9, 17-20]. Details of the treatment schedules along with study en-points and molecular analysis performed are reported in the online supplement. [9,19,21].

Long-term follow-up and statistical analysis

The update was made by taking information from 28 out of 29 participating centers regarding the clinical status of each patient entered in the prospective trial: status alive or dead or lost to follow-up, with the date of death or last follow-

up alive; cause of death, i.e., lymphoma progression, secondary neoplasm, non-neoplastic late fatal complications, or other causes; occurrence of secondary hematopoietic or non-hematopoietic neoplasm; or disease status at last follow-up alive, i.e., continuous first, second or more CR

In the present update, alive patients were censored at the date of last contact (February 2, 2017), providing a median EFS and OS follow-up time of 13.01 years (range 0.5-16.6, interquartile range 11.8-14.7). All analyses were done on an intention-to-treat basis.

Survival curves were estimated by the Kaplan Meier method according to the revised response criteria published in 2007 and compared using the log-rank test [22-24]. EFS, OS, PFS, and DFS were analyzed by the Cox proportional hazards model, comparing the two treatment arms (R-CHOP vs. R-HDS) by the Wald test and calculating 95% confidence intervals [25].

The cumulative incidences (CIs) of sMDS/AML and solid malignancies in the whole cohort and stratified by the treatment arm were estimated at 5, 10, and 13 years from diagnosis were assessed by the Gray test [26]. All reported P values were two-sided, at the conventional 5% significance level. Data were analyzed as of January 2018 using R 3.4.3 [27].

RESULTS

OS and causes of death

As of February 2017, 88 (66%) patients were alive at their last follow-up. Overall, median survival had not yet been reached at the 13-year median follow-up, with a 13-year OS estimate of 66.4% for the whole patient cohort. Similar OS values were observed in the two treatment arms, with 13-year OS estimates of 68.5% and 64.5% for patients in the CHOP-R and R-HDS arms, respectively (Figure 1).

At the latest follow-up, 46 patients had died. The main causes of deaths were disease progression for 22 patients (16.4% of the whole series, 47.8% of all deaths); secondary malignancies (three solid tumor, nine sMDS/AML) for 12 patients (8.9% of the whole series, 26.1% of all deaths); 12 patients died for various causes, including six fatal cardiovascular events, three documented infections, one graft failure following autograft, one anaphylactic shock following Ig i.v. infusion, and one late sudden death. Among patients in the CHOP-R arm, 13 out of 20 (65%) died from disease-related causes, whereas lymphoma progression was the cause of death for 9 out of 26 (35%) patients in the R-HDS arm. Main causes of death per each treatment arm are summarized in Figure 2.

CR and MR: achievement and durability

CR was documented in 98 (73.1%) patients: 39 (59.1%) of 66 undergoing CHOP-R treatment and 59 (86.7%) of 68 R-HDS-treated patients. CR achievement had a significantly favorable impact on survival, with 13-year OS estimates of 77.0% and 36.8%, for CR vs. no-CR achievement, respectively (Figure 3A). Moreover, a durable CR was associated with prolonged survival. Overall, of 79 patients in CR at 2 years since treatment initiation, 65 (82.3%) were alive at 13 years compared to 21 (58.3%) among 36 patients with early relapse (p=0.003).

MR was documented in 39 (65%) out of 60 evaluable patients: 11 (44%) of 25 undergoing CHOP-R treatment and 28 (80%) out of 35 R-HDS-treated patients (p<0.001) [9]. Again, MR achievement was associated with a superior OS compared

to patients not in MR following treatment (13-year OS estimates of 82.1% and 51.9%, for MR vs. no-MR achievement, respectively; Figure 3B).

Overall, 50 patients (37.3% of the whole series) were alive at this follow-up without any disease recurrence (18 in the CHOP-R and 32 in the R-HDS arms) since their first CR achievement. Among 98 patients obtaining CR, 39 had disease recurrence (39.8%). In the CHOP-R and R-HDS arms, the last disease recurrence respectively was recorded at 10 years and at 7 years from CR achievement. In addition, there were nine late toxic events (one in CHOP-R and nine in R-HDS) in patients in their first continuous CR. For patients reaching CR, the DFS estimate was 57.9% at 13 years. The 13-year DFS estimate was 47.1% for the 39 patients in CR following CHOP-R and 65.3% for the 59 patients in CR following R-HDS (Figure 4).

A subgroup of patients was further monitored for their molecular disease at long-term. After a median of 4 years of molecular monitoring since treatment completion, of the 24 patients alive in their first CR and evaluable for molecular disease, 20 (83%) patients were still in their first MR.

The 13-year estimates for EFS and PFS were 37.3% and 46.3% among all patients, respectively. Both EFS and PFS curves remained significantly superior in the R-HDS compared to CHOP-R arm. For CHOP-R and R-HDS, 13-year EFS estimates were respectively 26.6% (median EFS: 1.6 years) and 48.5% (median EFS: 7.4 years) (Figure 5 A). The 13-year PFS estimates were 28.8% (median PFS: 1.9%) and 59.1% (median PFS: not reached), for the CHOP-R and R-HDS arms, respectively (Figure 5 B).

Rescue of patients with refractory and relapsed disease

Overall, 72 patients (53.7%) had disease progression (45 CHOP-R and 27 R-HDS), following PR or refractory disease after induction (33 patients) or recurrence after CR achievement (39 patients). Five patients had progression with documented histological transformation and four with central nervous system involvement. As of the last follow up, 38 (52.8%) out of 72 progressing patients were long-term

survivors following salvage therapies after disease recurrence. Among rescued patients, 28 patients were in the CHOP-R and 10 in the R-HDS arms. At the last follow-up, besides the 50 patients alive in their first CR, 20 patients were long-term survivors in their second CR (14 CHOP-R and 6 R-HDS) and 18 were surviving beyond a second CR (14 CHOP-R and 4 R-HDS).

High-dose therapy and autograft were employed as salvage therapy in 28 patients with disease progression following initial CHOP-R. Nineteen of them at this follow-up were long-term survivors, with a median PFS-2 of 6.2 years. Nine patients eventually died because of lymphoma (seven patients) or secondary malignancy (two patients). Allogeneic stem cell transplant was employed as the ultimate rescue approach in five patients; two of them were long-term survivors at this follow-up, while three died (one from graft-versus-host disease, one from lymphoma progression, and one from a secondary tumor).

Factors affecting long-term survival

In univariate analysis, the main features at disease presentation and treatment end that significantly favored long-term survival were female sex, age <50 years, treatment completion, MR and CR (see Table 2). When these factors were evaluated in multivariate analysis, CR still showed a strong impact along with a borderline value for female sex (Table 2). When PCR status (assay performed on 60 patients only) was excluded from the multivariate analysis, CR was still the strongest factor favorably affecting survival. In addition, younger age had a strong significant impact along with female sex (Table 2).

Secondary tumor occurrence

The respective cumulative incidences of sMDS/AL at 5, 10, and 13 years were 5.9%, 8.9% and 10.5% for the R-HDS arm and 0.0%, 10.7%, and 10.7%, respectively, for the CHOP-R arm (p=0.832). The respective cumulative incidences of secondary non-MDS/AL neoplasms at 5, 10, and 13 years were 5.9%, 10.4%, and 11.9% for the R-HDS arm and 0%, 4.9%, and 8.8% for the CHOP-R arm (p=0.792). Secondary neoplasms in the R-CHOP arm were carcinomas (five total: two laryngeal, two urothelial, one pacreatic), Hodgkin's lymphomas (two), MDS (two total, one of which evolved in LAM), AML (one), and LAL Ph+ (one). In the R-

HDS arm, we observed five carcinoma cases (three head-and-neck, one mammary, one gastric), one non-melanoma skin cancer, one plasma cell dyscrasia, four MDS cases, and four AMLs.

DISCUSSION

The present study reports outcomes after a median 13 years of follow-up of a multicenter prospective trial comparing high-dose chemotherapy and autograft vs. CHOP chemotherapy, both delivered with rituximab (R-HDS vs CHOP-R), as upfront therapy in high-risk FL patients. To our knowledge, this follow-up is the longest ever reported for first-line treatment of FL with rituximab-supplemented chemotherapy. The prolonged observation shows an extraordinary improvement in overall survival compared to the pre-rituximab era [15,16]. The survival was similar in both treatment arms, confirming over the long-term our preliminary observation that R-HDS does not add survival advantages compared to CHOP-R in the upfront therapy of high-risk FL [9]. CR achievement was the most important factor for prolonged survival. The importance of disease response is further emphasized by the first-time observation that MR achievement is associated with survival duration and a high proportion of patients had prolonged survival in the absence of disease recurrence.

The GITMO-IIL trial was designed for patients with high-risk FL, histologically diagnosed according to the REAL/WHO lymphoma classification [14]. The FL diagnosis was confirmed by the high rate of BCL-2 gene translocation detected in patients with molecular assessment. The high-risk presentation was proved using the clinical prognostic scores available when the protocol was designed [15-16]. The subsequently developed FLIPI score employs other clinical parameters, and a proportion of our patients were not true “high risk” according to FLIPI [28]. Nevertheless, all study patients clearly belonged to a severely ill population, with a 5 year survival expectancies of 43.6% (aaIPI score) and 38% (ILI score), according to treatment available at the time the trial was conceived [15-16]. The 13-year survival of 66.4% recorded in our series represents a marked improvement in life expectancy compared to survival reported in the pre-rituximab era for similar high-risk FL patients. This result is especially notable because only four rituximab doses were applied to the majority of patients, and the treatment schedule was not that most frequently delivered in present times.

Recently, two other prospective trials performed in advanced-stage FL with

rituximab-based upfront regimens have been updated, i.e. the Italian FOLL05 study comparing R-CVP, R-CHOP, and R-FM and the SWOG study comparing R-CHOP vs. CHOP followed by radioimmunotherapy [29-30]. Both the FOLL05 study, with 8-year OS of 83%, and the SWOG study, with 10-year OS of 78%, showed extended life expectancies in the absence of rituximab maintenance. These values are in line with our 13-year OS of 66% obtained in a selected group of high-risk FL. The results strengthen the observations from several retrospective studies showing prolonged survival in FL following immunochemotherapy [10-13]. Moreover, results from all of these studies indicate that the CHOP schedule delivered with rituximab is currently the first choice for the upfront treatment of advanced stage FL, ensuring prolonged survival, with adequate information about possible late side effects.

In our whole series lymphoma progression remained the most frequent cause of failure, accounting for 47.8% of all causes of death, in line with several previous observations, including a recent report on a large series of FL [31]. Indeed, lymphoma progression was much more often responsible for fatal outcome among patients allocated to the CHOP-R arm, with 65% of deaths, compared to the R-HDS arm with only 35% of deaths. On the other hand, early and late toxicities were the most frequent cause of failure for patients in the R-HDS arm, which counterweighed the increased anti-lymphoma activity of R-HDS compared to CHOP-R, resulting in analogous overall survival for the two treatment arms. Rituximab maintenance is now employed with the aim of reducing disease recurrence risk [32]. In addition, both bendamustine and the novel anti-CD20 obinutuzumab antibody have been proposed as more effective first-line treatments compared to R-CHOP [33-34]. In particular, Bendamustine is now frequently employed as first-line treatment in place of the CHOP schedule. However, no evidence is currently available to suggest that these novel treatment strategies will substantially reduce the risk for disease-related deaths without affecting the treatment safety profile at long-term. Indeed, our update reinforces the need for prolonged observation to define the true survival advantage of any novel treatment for FL. Novel treatments for FL should combine potent anti-lymphoma activity along with low risk of both early and late toxicities.

Most late toxicities were secondary malignancies associated with the use of high-dose therapy with autograft delivered either upfront in the R-HDS arm or as salvage therapy in a good proportion of patients failing after upfront CHOP-R. This finding is in line with previous reports, including a retrospective study from GITIL group indicating increased risk for secondary MDS/AL in lymphoma patients receiving high-dose therapy and autograft [35]. A recent surveillance study by the Spanish GELTAMO group has further stressed the risk of secondary MDS/AL in FL patients undergoing autograft [36]. Moreover, both the GITIL and GELTAMO studies indicated a trend for increased risk for secondary solid tumors when autograft is delivered along with rituximab [35-36]. Thus, the risk for late occurrence of secondary malignancy is a main issue in the long-term management of FL patients. This concern must be kept in mind in the long-term assessment of the efficacy of novel drugs and drug combinations [33-34; 37-39].

The present study allows identification of the factors favoring the long-term survival of high-risk FL patients treated with rituximab-containing chemotherapy. Somewhat unexpectedly, CR achievement proved to be the strongest prerequisite for long-term survival. Several recent observations indicate that response to initial treatment along with the achievement of a strong and durable response may favorably affect long-term outcome [31, 40-44]. The present update clearly demonstrates in a prospective study that CR achievement shows the strongest association with prolonged survival. The importance of the response depth for long-term survival is confirmed by our molecular monitoring of MRD performed in a subset of patients. Most studies have shown a remarkable prognostic value of MRD assessment in terms of PFS and response duration [9, 17, 20, 45-46]. Nevertheless, the impact on OS could not be fully addressed in most studies, usually because of inadequate follow-up [47-48]. Here, it was possible to demonstrate for the first time that MRD assessment is predictive for both PFS and OS and that MR was associated with a prolonged survival.

The association of response depth with long-term survival in our FL series is further substantiated by the observation that a good proportion of patients, around 37% of the whole series, could survive in their first CR at long term. The

DFS curves were definitely promising, with a 13-year estimate as high as 65% in R-HDS-treated patients. Moreover, most patients achieving MR following induction treatment maintained their MR during long-term molecular monitoring. Taken together, these results indicate that an extensive disease response in FL may translate into both prolonged survival and in the long-term persistence of CR, a state that has been described as functional cure in other clinical settings. This in turn raises the issue of the curability of FL, at least in patients with a high-risk clinical presentation such as those selected in the present study.

ACKNOWLEDGMENTS

This work was supported in part by the Ministero Italiano Università e Ricerca (MIUR), Rome, Italy (grant PRIN 2010-2011, *pr. N.: 2010B5B2NL*), and by Banca del Piemonte (Torino, Italy). The initial clinical trial (March 2000 - May 2005) was made possible by Compagnia di San Paolo (Torino, Italy), Regione Piemonte (Torino, Italy), and by Roche (Milan, Italy), which provided free rituximab for all patients. We are indebted to GITMO (Gruppo Italiano Trapianto Midollo Osseo) and to IIL, now merged into FIL (Fondazione Italiana Linfomi) for their fundamental participation in the development and completion of the study.

AUTHORSHIP CONTRIBUTIONS

R.B. and C.T. conceived the present study; the initial trial was designed by A.M.G., P.C., M.L. and C.T. (along with A. Pileri, now retired); F.B., C.B., C.P., A.M.B., A. P., M.M., A.M.L., G.G., C.C., F.R., F.C., D.R.S., C.S., F.D.R., A.T., L.D., V.Z., F.Z., F.N., A.D., G.P., G. S., F.L., T.P., F.A., A.B., A.R., A.M.G., P.C., M.L., and C.T. were involved in patient enrollment and care and clinical data updates; R.B., A.G., R. P. and C.T. perfomed data collection and analysis; molecular analysis was performed by B.M. and M.L. (responsible); R.P. performed the statistical analyses; CT wrote the paper; R.B., A.M.G, A.R., P.C., R.P., M.L. and C.T. supervised the analyses and reviewed the manuscript.

This trial was registered at www.clinicaltrials.gov as no. NCT00435955

REFERENCES

1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. B-cell lymphomas. Version 7.2017 — December 5, 2017. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed January 10, 2018.
2. Dreyling M, Ghielmini M, Rule S, et al, on behalf of the ESMO. Guidelines Committee. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann of Oncol. 2016;27(Supplement 5):v83–v90.
3. Corradini P, Ladetto M, Zallio F, et al. Long-term follow-up of indolent lymphoma patients treated with high-dose sequential chemotherapy and au- tografting: evidence that durable molecular and clinical remission frequently can be attained only in follicular subtypes. J Clin Oncol. 2004;22(8):1460-1468.
4. Lenz G, Dreyling M, Schiegnitz E, et al. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission pro- longs progression-free survival in follicular lymphoma: results of a prospective, randomized trial of the German Low-Grade Lymphoma Study Group. Blood. 2004;104(9):2667-2674.
5. Deconinck E, Foussard C, Milpied N, et al. High-dose therapy followed by autologous purged stem-cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by GOELAMS. Blood. 2005;105(10):3817-3823.
6. Hiddemann W, Buske C, Dreyling M, et al. Treatment strategies in follicular lymphomas: current status and future perspectives. J Clin Oncol. 2005;23(26):6394-6399.
7. Sebban C, Mounier N, Brousse N, et al. Standard chemotherapy with interferon compared with CHOP followed by high-dose therapy with autologous stem cell transplantation in untreated patients with advanced follicular lymphoma: the GELF-94 randomized study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA) Blood. 2006;108(8):2540–2544.
8. Brown JR, Feng Y, Gribben JG, et al. Long-term survival after autologous bone marrow transplantation for follicular lymphoma in first remission. Biol Blood Marrow Transplant. 2007;13(9):1057-1065.
9. Ladetto M, De Marco F, Benedetti F, et al. Prospective, multicenter randomized GITMO/IIL trial comparing intensive (R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: the superior disease control of R-HDS does not translate into an overall survival advantage. Blood. 2008;111(8):4004-4013.
10. Liu Q, Fayad L, Cabanillas F, et al. Improvement of overall and failure-free survival in stage IV follicular lymphoma: 25 years of treatment experience at The University of Texas M.D. Anderson Cancer Center. J Clin Oncol. 2006;24(10):1582-1589.

11. Schulz H, Bohlius JF, Trelle S, et al: Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: A systematic review and meta-analysis. J Natl Cancer Inst. 2007;99(9):706-714.

12. Tan D, Horning SJ, Hoppe RT, et al. Improvements in observed and relative survival in follicular grade 1-2 lymphoma during 4 decades: the Stanford University experience. Blood. 2013;122(6):981–987.

13. Nabhan C, Aschebrook-Kilfoy B, Chiu BC, Kruczek K, Smith SM, Evens AM. The impact of race, age, and sex in follicular lymphoma: a comprehensive SEER analysis across consecutive treatment eras. Am J Hematol. 2014;89(6):633-638.

14. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood. 1994;84(5):1361-1392.

15. López-Guillermo A, Montserrat E, Bosch F, Terol MJ, Campo E, Rozman C. Applicability of the International Index for aggressive lymphomas to patients with low-grade lymphoma. J Clin Oncol. 1994;12(7):1343-1348.

16. Federico M, Vitolo U, Zinzani PL, et al. Prognosis of follicular lymphoma: a predictive model based on a retrospective analysis of 987 cases Blood. 2000;95(3):783-789.

17. Rambaldi A, Lazzari M, Manzoni C, et al. Monitoring of minimal residual disease after CHOP and rituximab in previously untreated patients with follicular lymphoma. Blood. 2002;99(3):856-862.

18. Tarella C, Caracciolo D, Corradini P, et al. Long-term follow-up of advanced-stage low-grade lymphoma patients treated upfront with high-dose sequential chemotherapy and autograft. Leukemia. 2000;14(4):740-747.

19. Ladetto M, Corradini P, Vallet S, et al. High rate of clinical and molecular remissions in follicular lymphoma patients receiving high-dose sequential chemotherapy and autografting at diagnosis: a multicenter, prospective study by the Gruppo Italiano Trapianto Midollo Osseo (GITMO). Blood 2002;100(5):1559-1565.

20. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize re-sponse criteria for non-Hodgkin's lymphomas: NCI Sponsored International Working Group. J Clin Oncol. 1999;17(4):1244-1253.

21. Corradini P, Astolfi M, Cherasco C, et al. Molecular monitoring of minimal residual disease in follicular and mantle cell non-Hodgkin's lymphomas treated with high-dose chemotherapy and peripheral blood progenitor cell autografting. Blood. 1997;89(2):724-731.

22. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc. 1958;53(282):457-481.

23. Cheson BD, Pfistner B, Juweid ME, et al. International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-86.

24. Mantel H, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22(4):719-748.

25. Cox DR. Regression models and life tables. J Royal Stat Soc Series B.

1972;34:187-220.

26. Gray RS. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat. 1988;16(3):1141-1154.

27. R Foundation for Statistical Computing, Vienna-A, http://www.R-project.org

28. Solal-Celigny, P. Roy, P. Colombat, et al. Follicular lymphoma international prognostic index. Blood. 2004;104(5):1258-1265.

29. Luminari S, Ferrari A, Manni M, et al. Long-Term Results of the FOLL05 Trial Comparing R-CVP Versus R-CHOP Versus R-FM for the Initial Treatment of Patients With Advanced-Stage Symptomatic Follicular Lymphoma. J Clin Oncol. 2017;36(7):689-696.

30. Shadman M, Li H, Rimsza L, et al. Continued Excellent Outcomes in Previously Untreated Patients With Follicular Lymphoma After Treatment With CHOP Plus Rituximab or CHOP Plus 131I-Tositumomab: Long-Term Follow-Up of Phase III Randomized Study SWOG-S0016. J Clin Oncol. 2018;36(7):697-703.

31. Sarkozy C, Maurer MJ, Link BK, et al. Cause of Death in Follicular Lymphoma in the First Decade of the Rituximab Era: A Pooled Analysis of French and US Cohorts. J Clin Oncol, 2019;37(2):144-152.

32. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): A phase 3, randomised controlled trial. Lancet. 2011;377(9759):42-51.

33. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with in- dolent and mantle-cell lymphomas: An open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381(9873):1203-1210.

34. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med. 2017;377(14):1331-1344.

35. Tarella C, Passera R, Magni M, et al. Risk Factors for the Development of Secondary Malignancy After High-Dose Chemotherapy and Autograft, With or Without Rituximab: A 20-Year Retrospective Follow-Up Study in 1,347 Patients With Lymphoma. J Clin Oncol. 2011,29(7):814-824.

36. Jiménez-Ubieto A, Grande C, Caballero D, et al., on behalf of GELTAMO (Grupo Español de Linfomas y Trasplantes de Médula Ósea) Cooperative Study Group. Secondary malignancies and survival outcomes after autologous stem cell transplantation for follicular lymphoma in the pre-rituximab and rituximab eras: a long-term follow-up analysis from the Spanish GELTAMO registry. Bone Marrow Transplant. 2018;53(6):780-783.

37. Smith SM, Pitcher BN, Jung SH, et al. Safety and tolerability of idelalisib, lenalidomide, and rituximab in relapsed and refractory lymphoma: The Alliance for Clinical Trials in Oncology A051201 and A051202 phase 1 trials. Lancet Haematol. 2017;4(4):e176-e182.

38. Leonard JP, Jung SH, Johnson J, et al. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance). J Clin Oncol. 2015;33(31):3635-3640.

39. Davids MS, Roberts AW, Seymour JF, et al. Phase I first-in-human study of venetoclax in patients with relapsed or refractory non-Hodgkin lymphoma. J Clin Oncol. 2017;35(8):826-833.

40. Tarella C, Gueli A, Delaini F, et al. Rate of Primary Refractory Disease in B and T-Cell Non-Hodgkin's Lymphoma: Correlation with Long-Term Survival. PLoS One. 2014;9(9):e106745.

41. Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. J Clin Oncol. 2015;33(23):2516– 2522.

42. Shi Q, Flowers CR, Hiddemann W, et al. Thirty-Month Complete Response as a Surrogate End Point in First-Line Follicular Lymphoma Therapy: An Individual Patient-Level Analysis of Multiple Randomized Trials. J Clin Oncol. 2017;35(5):552-560.

43. Sorigue M, Mercadal S, Alonso S, et al. Refractoriness to immunochemotherapy in follicular lymphoma: predictive factors and outcome. Hematol Oncol. 2017;35(4):520-527

44. Provencio M, Royuela A, Torrente M, et al, on behalf of the Spanish Lymphoma Oncology Group. Prognostic value of event-free survival at 12 and 24 months and long-term mortality for non-Hodgkin follicular lymphoma patients: A study report from the Spanish Lymphoma Oncology Group. Cancer. 2017;123(19):3709-3716.

45. Gribben JG, Freedman AS, Neuberg D, et al. Immunologic purging of marrow assessed by PCR before autologous bone marrow transplantation for B-cell lymphoma. N Engl J Med. 1991;325(22):1525-1533.

46. Ladetto M, Lobetti-Bodoni C, Mantoan B, et al, onbehalf of Fondazione Italiana Linfomi. Persistence of minimal residual disease in bone marrow predicts outcome in follicular lymphomas treated with a rituximab-intensive program. Blood. 2013;122(23):3759-3766.

47. Gritti G, Pavoni C, Rambaldi A. Is There a Role for Minimal Residual Disease Monitoring in Follicular Lymphoma in the Chemo-Immunotherapy Era? Mediterr J Hematol Infect Dis. 2017;9(1):e2017010.

48. Casulo C, Nastoupil L, Fowler NH, Friedberg JW, Flowers CR. Unmet needs in the first-line treatment of follicular lymphoma. Ann Oncol. 2017;28(9):2094-2106.

Table 1. Main patient features at presentation according to last survival status

	All patients	Patients alive[1]	Patients dead[1]	P Value
All, n=	134	88	46	
M/F, n=	78/56	45/43	33/13	0.022
Age (y), *median* (range)	51 (22-59)	50 (22-59)	53 (35-59)	0.297
Histologic grade I-II, n (%)	98 (73)	65 (73)	33 (71)	0.792
aaIPI 2 or more, no. (%)	120 (89)	75 (85)	45 (98)	0.024
FLIPI 3 or more, n (%)	78 (58)	52 (59)	26 (56)	0.775
Ann Arbor stage IV, n (%)	118 (88)	76 (86)	41 (89)	0.648
B symptoms, n (%)	63 (47)	40 (46)	23 (50)	0.617
ECOG PS 2 or more, n (%)	80 (60)	49 (56)	31 (67)	0.189
Bulky disease, n (%)	75 (56)	51 (58)	24 (52)	0.522
Spleen involvement, n (%)	50 (37)	28 (32)	22 (48)	0.061
Bone marrow involvement, n (%)	113 (84)	72 (82)	41 (89)	0.269
Extranodal involvement, n (%)	42 (31)	29 (33)	13 (28)	0.578
Abnormal LDH, n (%)	65 (59)	38 (43)	22 (48)	0.608
Treatment arm (CHOP-R/R-HDS), n	66/68	46/42	20/26	0.371

[1]Status after 13 years of median follow up

LDH, lactate dehydrogenase

Table 2. Univariate and multivariate proportional hazard models for OS

	Univariate		Multivariate (with PCR)		Multivariate (without PCR)[1]	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Sex (F vs M)	0.46 (0.24-0.88)	0.019	0.38 (0.14-1.04)	0.06	0.43 (0.22-0.84)	0.013
Age (> 50 y vs < 50 y)	2.21 (1.18-4.15)	0.013	2.11 (0.79-5.66)	0.137	2.76 (1.45-5.23)	0.002
Spleen involvement (Yes vs No)	1.62 (0.9-2.9)	0.109	NA	--	NA	--
PCR (Pos vs neg)	2.26 (1.07-6.65)	0.036	0.94 (0.28-3.2)	0.919	--	--
Treatment completed (Y vs N)	0.39 (0.22-0.70)	0.002	0.49 (0.15-1.64)	0.248	0.56 (0.26-1.22)	0.139
Response (CR vs no CR)	6.61 (2.53-17.25)	<0.001	6.79 (2.66-17.32)	<0.001	3.82 (2.12-6.89)	<0.001
Arm (R-HDS vs CHOP-R)	1.21 (0.68-2.17)	0.524	NA	--	NA	--

[1]PCR data are available for a subgroups of 60 patients

NA = not included in the analysis

FIGURE LEGENDS

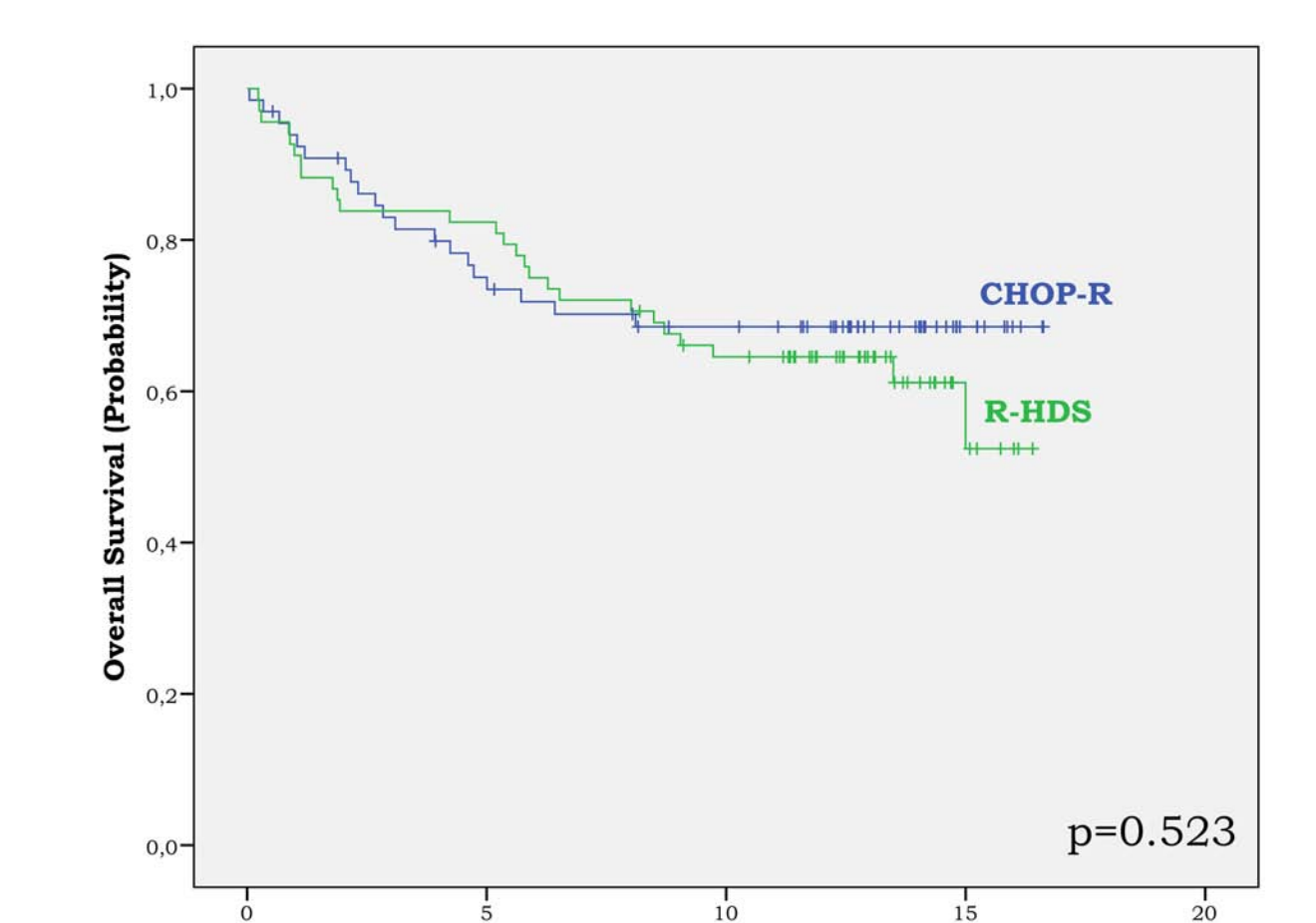
Figure 1. Updated overall survival (OS) according to treatment arms, i.e., intensive chemo-immunotherapy with autograft (R-HDS) vs. conventional chemoimmunotherapy (CHOP-R). Median follow-up: 13 years.

Figure 2. Main causes of death in the two treatment arms, including deaths due to: lymphoma, secondary malignancies (three solid tumor, nine sMDS/AML), non-malignant fatal events (six fatal cardiovascular complications, three documented infections, one graft failure following autograft) and other causes (not clearly related to treatment).

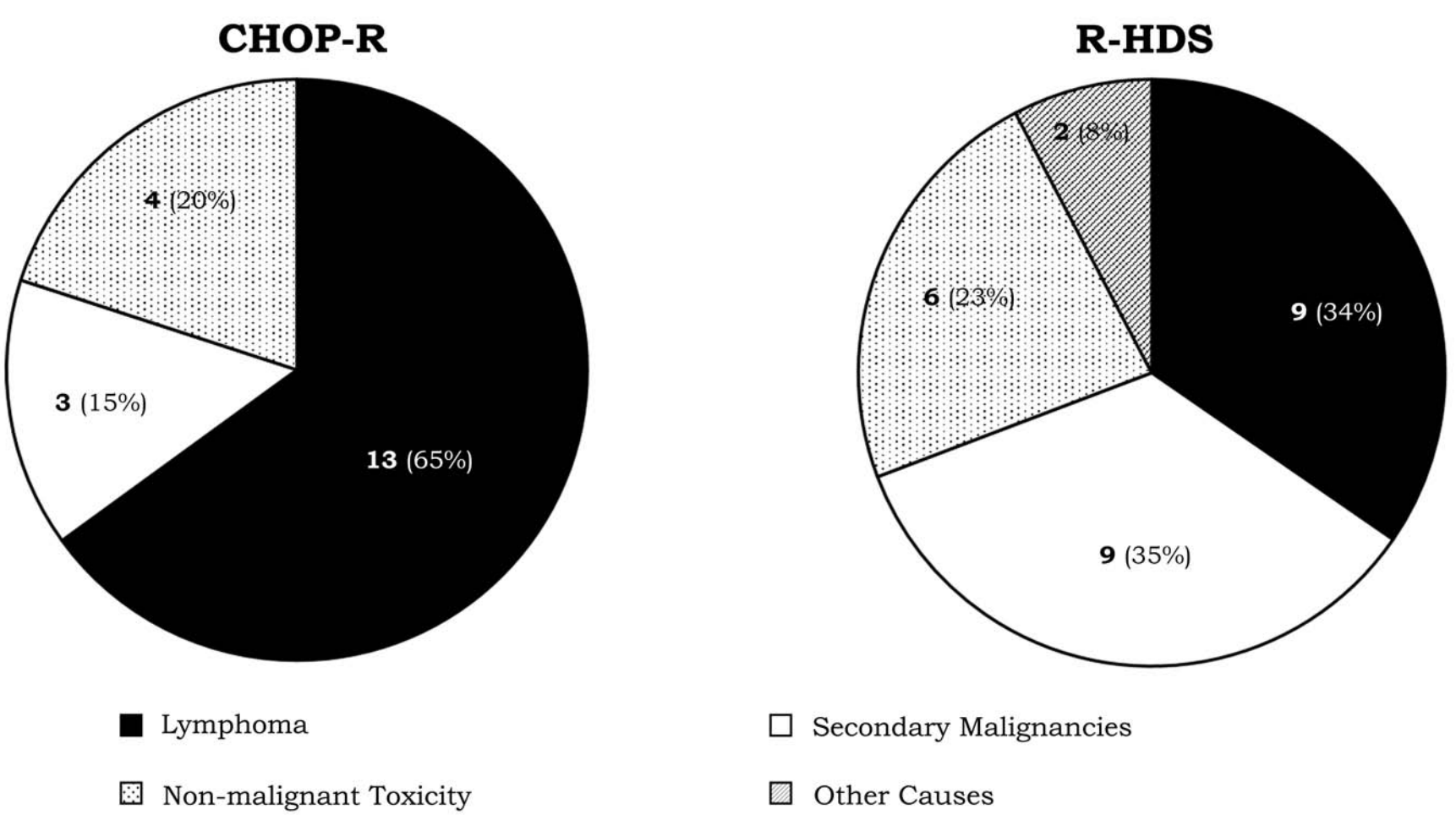
Figure 3. Updated overall survival according to end of treatment clinical status. ***A.*** Complete Remission (CR) achievement; ***B.*** molecular remission (PCR negative) achievement

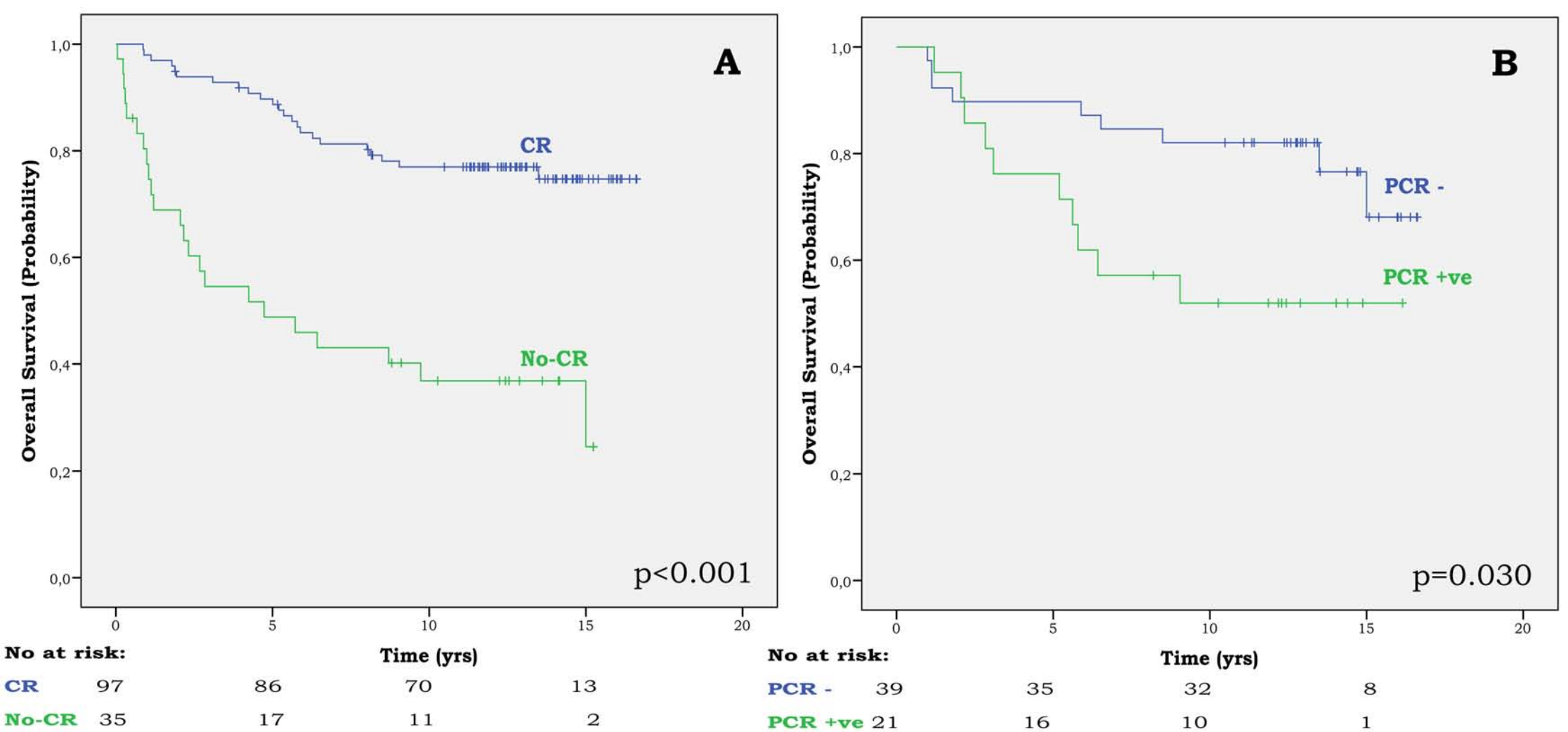
Figure 4. Updated disease-free survival (DFS) according to treatment arms, i.e., intensive chemo-immunotherapy with autograft (R-HDS) vs. conventional chemoimmunotherapy (CHOP-R)

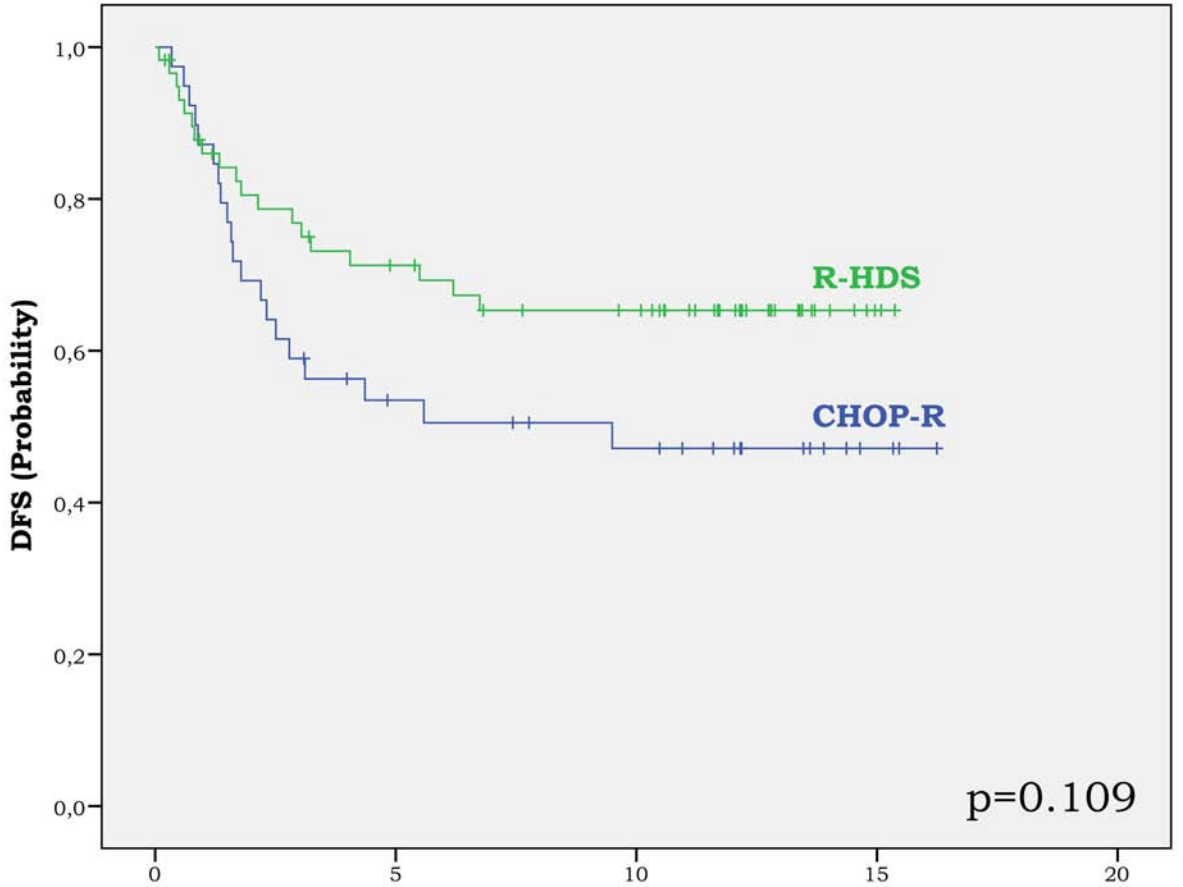
Figure 5. Updated event-free and progression-free survival according to treatment arms, i.e., intensive chemoimmunotherapy with autograft (R-HDS) vs. conventional chemoimmunotherapy (CHOP-R). ***A.*** event-free survival (EFS); ***B.*** progression-free survival (PFS)



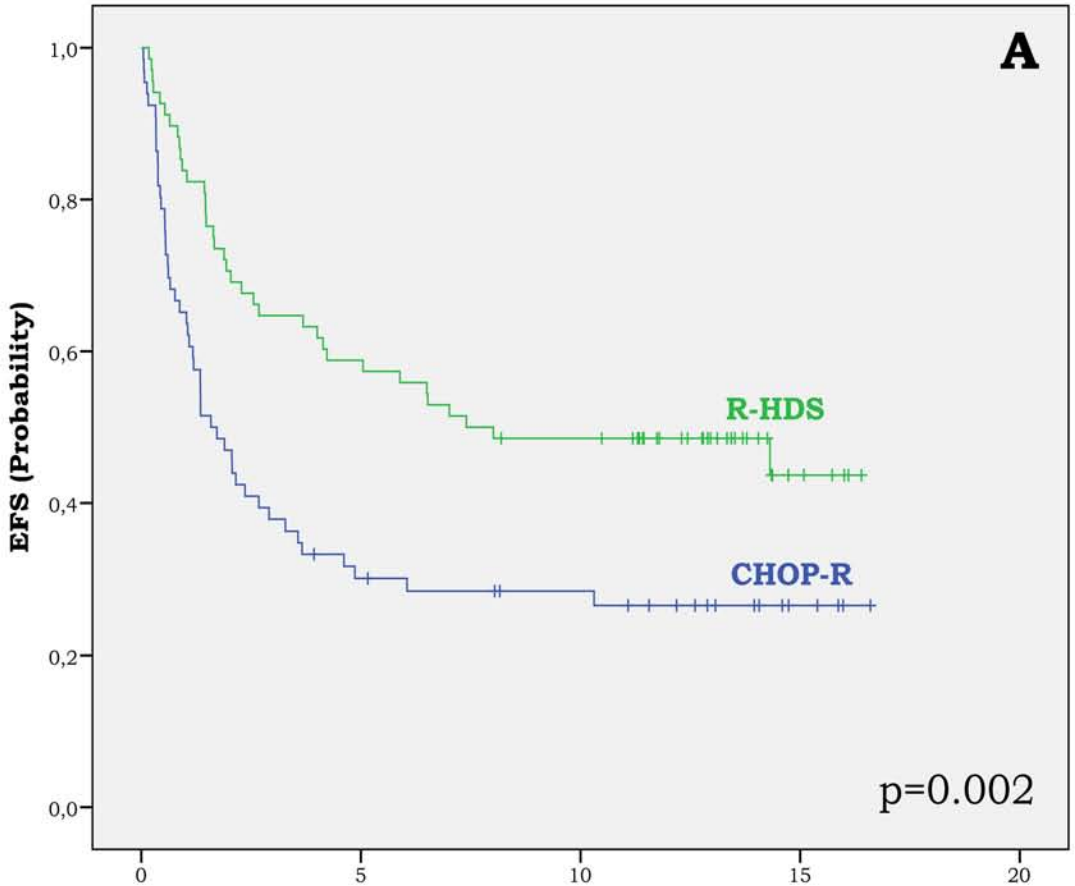
No at risk:				
CHOP-R	66	47	39	9
R-HDS	68	56	42	6

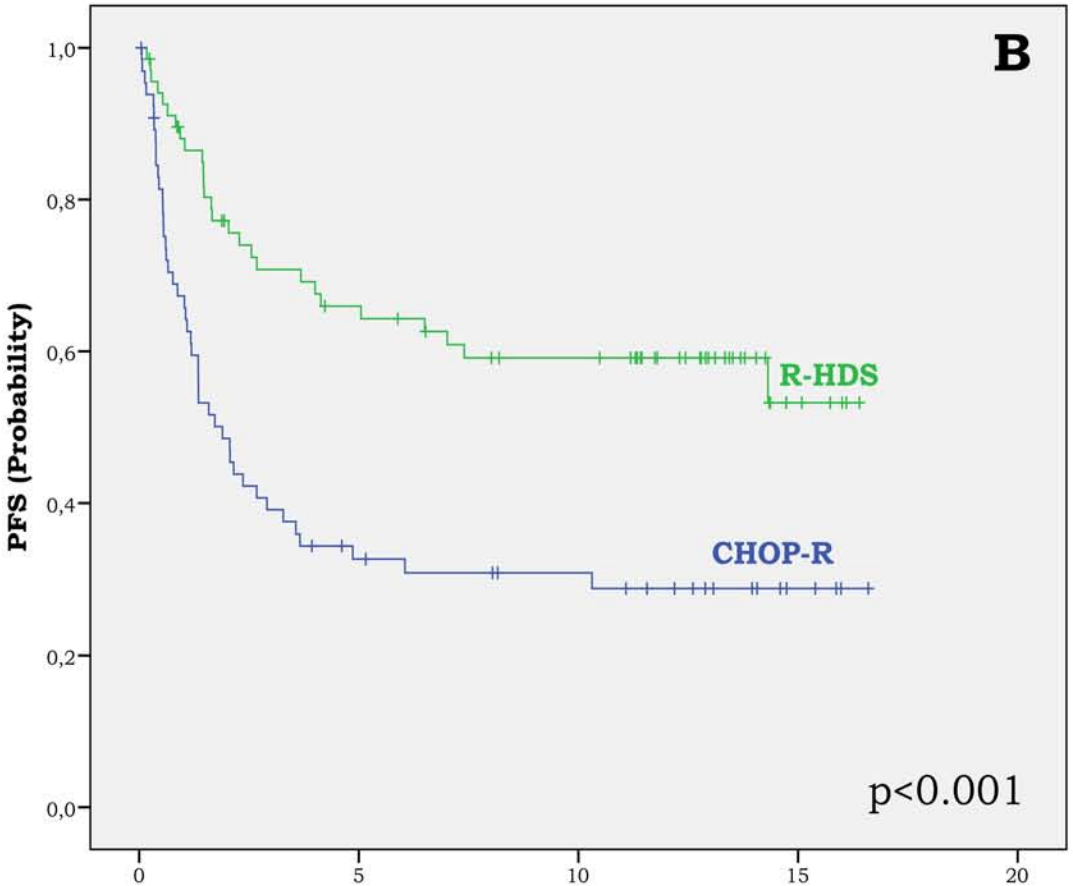

CHOP-R
4 (20%)
3 (15%)
13 (65%)
R-HDS
2 (8%)
6 (23%)
9 (34%)
9 (35%)
Lymphoma
Non-malignant Toxicity
Secondary Malignancies
Other Causes


A
Overall Survival (Probability)
1,0
0,8
0,6
0,4
0,2
0,0
CR
No-CR
p<0.001
0
5
10
15
20
Time (yrs)
No at risk:
CR 97 86 70 13
No-CR 35 17 11 2
B
Overall Survival (Probability)
1,0
0,8
0,6
0,4
0,2
0,0
PCR -
PCR +ve
p=0.030
0
5
10
15
20
Time (yrs)
No at risk:
PCR - 39 35 32 8
PCR +ve 21 16 10 1



No at risk:				
CHOP-R	39	18	14	3
R-HDS	59	37	30	2





No at risk:				
CHOP-R	66	19	15	4
R-HDS	68	40	32	5

No at risk:				
CHOP-R	66	19	15	4
R-HDS	68	40	32	5

METHODS: ADDITIONAL DETAILS

Patient characteristics

Between March 2000 and May 2005, a total of 136 patients were enrolled in the multicenter randomized study, launched in Italy among centers affiliated with GITMO (Gruppo Italiano Trapianto Midollo Osseo) and/or to the Italian Lymphoma Intergroup known as IIL (now incorporated into FIL, Fondazione Italiana Linfomi) [9]. All recruiting Centers were qualified by GITMO to perform autologous stem cell transplantation. The study was specifically designed for the first-line treatment of patients with a histologically proven diagnosis of FL according to the Revised European-American Lymphoma/World Health Organization (REAL/WHO) lymphoma classification (grades I, II, and III; patients with grade IIIb were not excluded) [14]. Patients aged 16 to 60 years were eligible if they had Ann Arbor stage III or IV and a high-risk prognostic presentation, according to the prognostic risk scores in use at the time the protocol was designed, i.e. the age-adjusted IPI score (score of 2 or greater) and the IIL score for FL (score 3 or greater) [15, 16]. As detailed in the CONSORT Diagram (online Supplement), 136 patients entered the study protocol; two patients in the CHOP-R arm were then excluded from the analysis: one patient withdrew the consent and one lacked a documented high-risk score. Main features of the 134 evaluable patients and of patients who are presently alive vs. those who have died since protocol entrance are reported in Table 1 in the text.

Study design and treatment schedule and end-points

The study aim was to assess the superiority of an intensive chemo-immunotherapy strategy including autologous hematopoietic stem cell transplantation (auto-HSCT) compared to conventional chemo-immunotherapy. Thus, following verification of eligibility criteria, a centralized computer generated a simple randomization sequence and patients were randomly assigned either to the intensified or conventional arm.

Briefly, the conventional arm consisted of six courses of CHOP chemotherapy,

followed by infusions of four weekly doses of 375 mg/m2 rituximab. The efficacy and feasibility of the sequential CHOP-R schedule for FL has been described by Rambaldi et al [17]. The intensified arm included the HDS schedule originally described for low-grade lymphoma, then supplemented with four doses of 375 mg/m2 rituximab (R-HDS) [18-19]. The R-HDS schedule consisted of three phases: (1) intensive debulking; (2) high-dose (HD) chemotherapy with stem cell collection of in vivo purged peripheral blood stem cells; and (3) auto-HSCT, as described previously [9, 18-19]. Two additional rituximab doses were planned in both arms (13 CHOP-R and 7 R-HDS patients) in case of partial remission (PR) or PCR positivity at the end of treatment. Moreover, consolidation radiotherapy was delivered to 31 (47%) CHOP-R and 28 (41%) R-HDS patients. The primary endpoint of the study was event-free survival (EFS), defined according to the 1999 Cheson criteria in use at that time, as detailed below in the "Statistical section" [20].

MRD assessment by nested PCR

Molecular analysis was performed in a central highly experienced translational laboratory, according to a previously described nested-PCR approach [9,19,21]. Overall, 104 patients had adequate diagnostic material for molecular evaluation and a molecular marker was identified in 73 patients (65 had translocated BCL2 and 8 clonal IGH gene rearrangement as molecular marker). Among 73 patients with a molecular marker, 13 were not assessed for the following reasons: early toxic death, no CR, and inadequate diagnostic material for subsequent assessment. Thus, molecular response was investigated in 60 patients.

Long-term follow-up

The first outcome analysis was performed in 2008 [9]. Overall, 134 high-risk FL cases were analyzed. Only two patients (both CHOP-R arm) were censored as "lost to follow-up" at the moment of analysis, after a follow-up of 23 and 6 months, respectively. Recently, the long-term outcome of patients enrolled in this prospecti ve study has been updated. As of February 2017, updated data were obtained from 28 out of 29 participating centers regarding 119 (87.5%) out of 134 evaluable patients of the study protocol. Patients alive at the last follow-up have been followed for a minimum of 11 years and up to a maximum of 16 years. Overall, besides the two patients lost to follow-up at 6 and 23 months,

respectively, three more patients were lost to follow-up while in CR at 4 and 5 years from therapy; an additional 10 patients were lost to follow-up while in CR after a minimum of 8 years or more since therapy. All 15 patients lost to follow-up at the final update in February 2017 were censored as "lost to follow-up" at the time of their last contact.

The update was made by taking information on the following from 28 out of 29 participating centers regarding the clinical status of each patient entered in the prospective trial: status alive or dead or lost to follow-up, with the date of death or last follow-up alive; cause of death, i.e., lymphoma progression, secondary neoplasm, non-neoplastic late fatal complications, or other causes; occurrence of secondary hematopoietic or non-hematopoietic neoplasm; or disease status at last follow-up alive, i.e., continuous first, second or more CR

Study end-point and statistical analysis

The primary end-point was originally established as event-free survival (EFS), defined as the time from entry into the clinical trial and random assignment until progression/relapse/death from any cause, whichever occurred first, according to criteria published at the time of study launch [20]. A sample size of 246 patients (123 per arm) had been calculated to detect a 20% absolute increase (from 35%-55%) in 3-year EFS. A single interim analysis was planned, including the 120 patients who completed the treatment before March 24, 2005. R-HDS showed a significant EFS improvement (29% absolute increase, from 35%-64%), compared to CHOP-R ($p < 0.001$); this result led the steering committee to stop enrollment on May 30, 2005 [9].

Secondary end-points, again in the original protocol, were Overall Survival (OS), progression-free survival (PFS), and disease-free survival (DFS) [20]. The DFS curves for patients who achieved CR were calculated from CR date to relapse, death from lymphoma, or the last day of follow-up. Other secondary end-points were response rate, cumulative incidence of secondary myelodysplasia/acute myeloid leukemias (sMDS/AML) and solid tumors, rate of molecular remission (MR), and its impact on PFS. Alive patients were censored at the date of last contact (February 2, 2017), providing a median EFS and OS follow-up time of

13.01 years (range 0.5-16.6, interquartile range 11.8-14.7). All analyses were done on an intention-to-treat basis.

Survival curves were estimated by the Kaplan Meier method according to the revised response criteria published in 2007 and compared using the log-rank test [22-24]. EFS, OS, PFS, and DFS were analyzed by the Cox proportional hazards model, comparing the two treatment arms (R-CHOP vs. R-HDS) by the Wald test and calculating 95% confidence intervals [25]. The following covariates were tested as risk factors: age, sex, treatment arm, histologic grade, Ann Arbor stage, aaIPI score, FLIPI score (retrospectively assigned), "B" symptoms, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase, bulky disease (>5 cm diameter), spleen, bone marrow and extranodal involvement, MR rate, and achievement of CR/CR unconfirmed only for OS (this predictor was treated as a time-dependent covariate).

The cumulative incidences (CIs) of sMDS/AML and solid malignancies in the whole cohort and stratified by the treatment arm were estimated at 5, 10, and 13 years from diagnosis. The Gray test was used to compare the CI curves in the presence of a competing risk (defined as death from any cause except for sMDS/AML or solid tumors) [26].

Patient characteristics were estimated using the Mann Whitney test for continuous variables and the Fisher's exact test for categorical ones; all descriptive results for continuous variables are expressed as the medians (ranges).

All reported P values were two-sided, at the conventional 5% significance level. Data were analyzed as of January 2018 using R 3.4.3 [27].

CONSORT DIAGRAM, detailing the progress of 136 enrolled patients through the phases of the randomised trial