Response-Adapted Postinduction Strategy in Patients With Advanced-Stage Follicular Lymphoma: The FOLL12 Study

(Article begins on next page)

06 February 2025

Response-Adapted Postinduction Strategy in Patients With Advanced-Stage Follicular Lymphoma: The FOLL12 Study

Stefano Luminari 1 2, Martina Manni 1, Sara Galimberti 3, Annibale Versari 4, Alessandra Tucci 5, Carola Boccomini 6, Lucia Farina 7, Jacopo Olivieri 8, Luigi Marcheselli 9, Luca Guerra 10 11, Simone Ferrero 12, Luca Arcaini 13, Federica Cavallo 12, Sofya Kovalchuk 14, Tetiana Skrypets 1 15, Ilaria Del Giudice 16, Stephane Chauvie 17, Caterina Patti 18, Caterina Stelitano 19, Francesca Ricci 20, Antonello Pinto 21, Gloria Margiotta Casaluci 22, Vittorio R Zilioli 23, Anna Merli 24, Marco Ladetto 25 26, Silvia Bolis 27, Vincenzo Pavone 28, Annalisa Chiarenza 29, Annalisa Arcari 30, Antonella Anastasia 5, Alessandra Dondi 9, Donato Mannina 31, Massimo Federico 1; Fondazione Italiana Linfomi

1Surgical, Medical and Dental Department of Morphological Sciences Related to Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy.

2Azienda Unita Sanitaria Locale-IRCCS, Arcispedale Santa Maria Nuova-Ematologia, Reggio Emilia, Italy.

3Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy.

4Nuclear Medicine Division, Azienda USL IRCCS of Reggio Emilia, Reggio Emilia, Italy.

5ASST Spedali Civili di Brescia-Ematologia, Brescia, Italy.

6A.O.U. Città della Salute e della Scienza di Torino-SC Ematologia, Torino, Italy.

7Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Division of Hematology, Milano, Italy.

8Azienda Sanitaria Universitaria Friuli Centrale (ASU FC), SOC Clinica Ematologica, Udine, Italy.

9Fondazione Italiana Linfomi Onlus, Modena, Italy.

10School of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy.

11Nuclear Medicine, San Gerardo Hospital, ASST Monza, Italy.

12A.O.U. Città della Salute e della Scienza di Torino, Ematologia Universitaria, Torino, Italy.

13IRCCS Policlinico S. Matteo di Pavia, Div di Ematologia, Pavia, Italy.

14Azienda Ospedaliera Universitaria Careggi, Unità funzionale di Ematologia, Firenze, Italy.

15Clinical and Experimental Medicine (CEM), University of Modena and Reggio Emilia, Modena, Italy.

16Policlinico Umberto I, Università "La Sapienza," Istituto Ematologia, Dipartimento di Medicina Traslazionale e di Precisione, Roma, Italy.

17Medical Physics Division, Santa Croce e Carle Hospital, Cuneo, Italy.

18A.O. Ospedali Riuniti Villa Sofia-Cervello, Div di Ematologia, Palermo, Italy.

19Grande Ospedale Metropolitano Bianchi Melacrino Morelli-Ematologia, Reggio Calabria, Italy.

20Istituto Clinico Humanitas, U.O. Ematologia, Rozzano, Italy.

21Istituto Nazionale Tumori, IRCCS Fondazione G. Pascale, UOC Ematologia Oncologica, Napoli, Italy.

22AOU Maggiore della Carità di Novara, SCDU Ematologia, Novara, Italy.

23ASST Grande Ospedale Metropolitano Niguarda, SC Ematologia, Milano, Italy.

24Ospedale degli Infermi di Rimini, U.O. di Ematologia, Rimini, Italy.

25Dipartimento di Medicina Traslazionale Università del Piemonte Orientale, Alessandria, Italy.

26SC Ematologia, AO SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy.

27SC di Ematologia, ASST MONZA, Monza, Italy.

28A.O. C. Panico, U.O.C Ematologia e Trapianto, Tricase, Italy.

29A.O.O. Policlinico "G. Rodolico-S. Marco," U.O.C. Ematologia, Catania, Italy.

30Ospedale Guglielmo da Saliceto, U.O.Ematologia, Piacenza, Italy.

31Azienda Ospedaliera Papardo-UOC di Ematologia, Messina, Italy.

Abstract

PURPOSE

We compared 2 years of rituximab maintenance (RM) with a response-adapted postinduction approach in patients with follicular lymphoma who responded to induction immunochemotherapy.

METHODS

We randomly assigned treatment-naïve, advanced-stage, high-tumor burden follicular lymphoma patients to receive standard RM or a response-adapted postinduction approach on the basis of metabolic response and molecular assessment of minimal residual disease (MRD). The experimental arm used three types of postinduction therapies: for complete metabolic response (CMR) and MRD-negative patients, observation; for CMR and MRD-positive (end of induction or follow-up) patients, four doses of rituximab (one per week, maximum three courses) until MRD-negative; and for non-CMR patients, one dose of

ibritumomab tiuxetan followed by standard RM. The study was designed as noninferiority trial with progression-free survival (PFS) as the primary end point.

RESULTS

Overall, 807 patients were randomly assigned. After a median follow-up of 53 months (range, 1-92 months), patients in the standard arm had a significantly better PFS than those in the experimental arm (3-year PFS 86% v 72%; P < .001). The better PFS of the standard versus experimental arm was confirmed in all the study subgroups except non-CMR patients (n = 65; P = .274). The 3-year overall survival was 98% (95% CI, 96 to 99) and 97% (95% CI, 95 to 99) in the reference and experimental arms, respectively (P = .238).

CONCLUSION

A metabolic and molecular response-adapted therapy as assessed in the FOLL12 study was associated with significantly inferior PFS compared with 2-year RM. The better efficacy of standard RM was confirmed in the subgroup analysis and particularly for patients achieving both CMR and MRD-negative.

INTRODUCTION

The use of the monoclonal anti-CD20 antibody rituximab (R) has improved the outcome of patients with newly diagnosed follicular lymphoma (FL).[1–3] R is currently used in combination with chemotherapy for the induction treatment of patients with high-tumor burden FL and is recommended for 2-year maintenance treatment in patients responding to induction immunochemotherapy (ICT).[4,5] The use of R for maintenance treatment is based on a formal demonstration of its ability to reduce the risk of FL progression compared with observation only.[5–8] However, lacking a similar effect on the overall survival (OS) efforts to better predict the individual risk of failure in patients with FL early in the course of disease has become a key research priority in the field.

CONTEXT

Key Objective

The FOLL12 study has been conducted with the hypothesis that a fluorodeoxyglucose-positron emission tomography and minimal residual disease response–adapted postinduction management of patients with high-tumor burden follicular lymphoma (FL) responding to standard immunochemotherapy was noninferior in terms of progression-free survival compared with standard rituximab maintenance (RM).

Knowledge Generated

We demonstrated that (1) RM was better than the response-adapted management in terms of progression-free survival, (2) Standard RM reduced the risk of disease progression also for patients with the best quality of response, and (3) the lack of any overall survival difference between study arms.

Relevance (J.W. Friedberg)

The results of the FOLL12 trial do not support a response-adapted treatment paradigm in FL. Minimal residual disease needs further validation before being incorporated as an integral biomarker in future trials of FL.**Relevance section written by JCO Editor-in-Chief Jonathan W. Friedberg, MD.

Among the several prognostic factors and indices that have been correlated with patients' outcomes, recent data have demonstrated the prognostic role of metabolic or molecular response evaluated by using 18 F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) or by applying minimal residual disease (MRD), respectively. FDG-PET is now the recommended technique to define end-induction response on the basis of international criteria.9–12 MRD evaluation by polymerase chain reaction (PCR) targeting the BCL2-immunoglobulin heavy chain (IGH) rearrangement is the most widely used and standardized molecular approach in FL on the basis of the documentation of the independent predictive value of MRD detection in FL.13 MRD negativity in the bone marrow and peripheral blood has been strongly associated with a reduced risk of recurrence, and MRD reappearance during follow-up may anticipate clinical progression.14–17

Although the results of randomized trials have confirmed that rituximab maintenance (RM) improves patient outcomes, the question is whether there is an alternative to standard RM to manage postinduction treatment. To this end, there are convincing arguments to support the use of available methods to define the quality of response and to adapt the intensity of the intervention to an accurate assessment of FL response. The FOLL12 trial aimed to show the noninferiority of a response-adapted postinduction strategy on the basis of FDG-PET and MRD response assessment after ICT, with 2-year maintenance with rituximab in patients with previously untreated advanced FL. Here, we present the mature results of the study performed after a median follow-up of 50 months.18

METHODS

FOLL12 was a prospective randomized open-label multicenter phase III trial designed for patients with previously untreated FL. The study was conducted in compliance with the Declaration of Helsinki, was approved by the appropriate Research Ethics Committee, and required that each patient gives written informed consent before registration and random assignment (ClinicalTrials.gov identifier: NCT02063685).

The trial included previously untreated patients age 18-75 years with a histologically confirmed diagnosis of FL grade 1, 2, or 3a according to the WHO classification,19 Ann Arbor stage II-IV, Eastern Cooperative Oncology Group performance status of 0-2, and Follicular Lymphoma International Prognostic Index 2 (FLIPI2) of > 0. The complete list of eligibility criteria is listed in the Data Supplement (online only).

Random Assignment and Treatment Protocol

Eligible patients were centrally randomly assigned before treatment start and were stratified by FLIPI2 score (1-2 v 3-5).20

All patients received induction therapy with six cycles of R in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone or bendamustine (choice made by the local investigator) followed by two additional doses of R.

At the end of induction (EOI) ICT, response was determined by the local investigator by computed tomography (CT) scan according to the 2007 revised international criteria.[21] For the purpose of this study, EOI response was also assessed using FDG-PET and using BCL2/IGH MRD analysis by nested PCR on peripheral blood and bone marrow samples in patients with available molecular marker (MM). Both EOI FDG-PET and MRD analyses were conducted in a centralized laboratory (refer to the Data Supplement for details).

For all patients showing partial remission or complete remission at EOI CT scan, postinduction management was delivered according to random assignment. Patients randomly assigned to the reference arm were prescribed standard maintenance, which consisted of 12 doses of R administered at 375 mg/m 2 (one dose every 8 weeks).

For patients randomly assigned to the experimental arm, postinduction treatment was managed on the basis of metabolic response (MR) as defined by FDG-PET and MRD analysis (Data Supplement).

Patients with a complete metabolic response (CMR, Deauville score 1-3) who were MRD-negative by nested PCR were only observed and were followed up with MRD monitoring and CT scan at 6-month intervals for 2 years and then annually. Patients with CMR who were MRD-positive at EOI assessment or who turned MRD-positive during follow-up received four weekly rituximab doses before an additional MRD assessment as suggested by a previous experience.[22] The weekly dose of R was repeated until MRD negativity was achieved (one dose per week, maximum 12 R doses overall) or up to three times. Patients with CMR for whom a MM at baseline was not available remained under observation with regular follow-up.

Patients without CMR, regardless of their MRD status, received intensified treatment with radioimmunotherapy (RIT) with (90)Y-ibritumomab tiuxetan followed by RM every 2 months, for a total of 11 infusions.

Statistics and Assessment of Efficacy

The primary end point was progression-free survival (PFS), defined as the time from the date of study entry to the last follow-up or to one of the following events: disease progression or relapse confirmed at CT scan or to the date of death from any cause.

Additional study end points were OS, response, and toxicity.

The study was initially designed as a superiority trial. However, as the first interim monitoring showed a higher-than-expected rate of CMR, the study was amended to a noninferiority design (see the Data Supplement for details) that was based on the hypothesis that the primary end point was not inferior in the experimental versus the reference arm in terms of PFS. A total accrual of 770 patients with 387 expected failures was planned under H1 to give 83% power to demonstrate noninferiority between the two arms, with an increased risk of < 1.309 in the PFS failure rate (see the Data Supplement for statistical details).

RESULTS

Between December 2012 and March 2018, 807 patients were randomly assigned by 50 Italian institutions. Twenty-one (2.6%) patients were subsequently excluded, leaving 786 patients who were fully eligible, 393 in the reference arm and 393 in the experimental arm (Fig 1). The

two arms were balanced in terms of patient characteristics and response to induction treatment (Data Supplement).

Of these 744 patients, 712 achieved a response, defining an overall response rate of 96% (95% CI, 94 to 97).

After a median follow-up of 53 months (range, 1-92 months), 197 PFS events were recorded, including 186 disease progressions and 11 deaths for causes unrelated to lymphoma progression. Overall, the 3-year PFS was 79% (95% CI, 76 to 82): 86% (95% CI, 82 to 89) for the reference arm and 72% (95% CI, 67 to 76) for the experimental arm (Fig 2A). The experimental arm was worse than the reference arm, even given the noninferiority margin. The risk of progression was significantly higher for the experimental arm (hazard ratio, 1.92; 95% CI, 1.43 to 2.56, also when adjusted by FLIPI2 and induction treatment, P < .001).

Details on MR at EOI were available for 691 of 712 patients: CMR was confirmed in 628 (90%), whereas 65 patients had positive EOI FDG-PET (9%) and two patients had indefinite result. Overall, the 3-year PFS was 81% (95% CI, 77 to 84) and 60% (95% CI, 47 to 71) for patients with and without CMR, respectively (P < .001). Among patients with CMR, the 3-year PFS was 90% (95% CI, 86 to 93) and 72% (95% CI, 67 to 77) in the reference and experimental arms, respectively (P < .001; Fig 3A).

According to the intention-to-treat analysis, of the 65 patients who did not achieve CMR, the 3-year PFS for the 31 cases in the reference arm was 50% (95% CI, 32 to 66) and for the 34 cases in the experimental arm, it was 70% (95% CI, 51 to 82; P = .274; Fig 3B).

Overall MM was lacking in 334 of the 786 randomly assigned eligible patients. In the subgroup of 712 patients who responded to induction therapy, 300 were identified as no marker, and no further MRD analysis was conducted in this group. The absence of the baseline MM was not associated with a different PFS compared with patients with MM (data not shown).

Of the 345 patients with MM of the 628 who achieved a CMR, 299 were MRD-negative (87%) at EOI and 46 (13%) were MRD-positive. The 3-year PFS for MRD-negative patients was 92% (95% CI, 78 to 91) in the reference arm (n = 143) and 78% (95% CI, 61 to 77) in the experimental arm (n = 156; P < .001; Fig 3C).

During follow-up, 81 of the 299 (27%) MRD-negative patients became MRD-positive, at a median time from EOI of 14 months (range, 5-36 months): 26 patients in the reference arm and 55 in the experimental arm. Overall, 51 patients were MRD-positive in the reference arm and 76 in the experimental arm, of whom 46 received weekly rituximab according to protocol. After receiving weekly R, 26 of these 46 patients achieved a molecular response at the subsequent MRD time points. Of the 51 MRD-positive patients in the reference arm, 32 achieved negative MRD status at subsequent time points (Data Supplement).

Overall, the use of weekly R in MRD-positive patients in the experimental arm was associated with inferior 3-year PFS compared with that of MRD-positive patients in the reference arm (Fig 3D; P < .001).

The better performance of the reference arm over the experimental was consistent across all different subgroups in a post hoc exploratory analysis of patient subgroups categorized by age, sex, induction treatment, FLIPI and FLIPI2 scores, stage III-IV, and nodal areas (Fig 4).

At the time of current update, 30 deaths were recorded, of which 15 were associated with disease progression or recurrence. Other causes of death were secondary malignancies (n = 3, 10% [gastric cancer, lung cancer, and mesenchymal abdominal cancer]), sepsis (n = 5, 17%), heart failure (n = 1, 3%), central nervous system disease (n = 2, 6%), pulmonary edema (n = 1, 3%), and three with cause not reported (10%). The 3-year OS was 98% (95% CI, 96 to 99) in the reference arm and 97% (95% CI, 95 to 99) in the experimental arm (P = .238; Fig 2B).

Safety

The safety analysis was available for 786 patients in the induction phase and for 712 in the postinduction phase.

During the induction phase, no difference in toxicity was observed between the two study arms (Data Supplement).

During the postinduction phase, 254 events with any grade were reported. In patients with CMR after induction ICT, the most common grade 3-4 adverse event was neutropenia (13.0% v 3.6%, in reference and experimental arms, P < .001). In patients without CMR after induction ICT (n = 30 in the reference arm and n = 32 in the experimental arm), the most frequent grade 3-4 events were neutropenia (10.0% v 43.8%; P = .004) and thrombocytopenia (0% v 37.5%; P < .001; Table 2).

In the group of 712 patients analyzed for the principal end point of the study, 39 second malignancies (SM) were registered. Considering deaths as a competing risk, the overall 5-year cumulative incidence (CI) of SM was 6.4% (95% CI, 4.6 to 8.9; Data Supplement).

DISCUSSION

The FOLL12 prospective, randomized, open-label multicenter phase III trial was conducted to assess the efficacy of a response-adapted postinduction treatment in patients with FL who responded to ICT. The study demonstrated that our response-adapted postinduction therapy resulted in significant inferiority compared with standard maintenance in terms of 3-year PFS (86% v 72%), with a hazard ratio of 1.92. Inferiority of the response-adapted experimental arm was found in most subgroups and, in particular, in patients with the highest quality of response defined by both CMR and MRD negativity. On the basis of these results, we

conclude that patients with FL responding to induction ICT should be offered 2-year R maintenance to guarantee the lowest risk of lymphoma progression.

The FOLL12 findings require careful reflection to try to understand these negative results. The rationale of the FOLL12 was based on the confirmed correlation between either metabolic or molecular response and the risk of disease progression and of death[10,12,14,16,23] and on the suggested combined role of both parameters in improving the ability to predict patient outcomes.[24] The hypothesized success of our response-adapted approach was based on the combined efficacy of therapeutic intervention for non-CMR patients and for MRD-positive patients, as suggested by the promising results achieved in a previous experience of our group,[22,25] and of no intervention for patients with the best response defined by both CMR and MRD negativity, assuming that the risk of progression in the latter group could not be modified by maintenance therapy. In this context, the significant reduction in the risk of progression observed for the group of patients with both CMR and MRD negativity who received standard maintenance had the greatest impact on the trial results. Thus, even if we were able to confirm the role of MR in predicting the risk of FL progression, we nevertheless conclude that the better response as defined by FDG-PET was not enough to keep the risk of progression low without RM. In the setting of CMR, molecular assessment of response was not able to further contribute to our response-adapted approach. Indeed, most of the patients with CMR also achieved MRD negativity (87%), although those in the experimental arm still experienced a higher risk of progression, heralded by subsequent MRD reappearance. Interestingly, for the smaller subgroup of CMR/MRD-positive patients for whom weekly rituximab was administered in the experimental arm, treatment was still associated with inferior efficacy compared with RM. Further analyses are thus required to improve the favorable predictive value of a good response to ICT in FL and to implement novel algorithms able to capture the concept of MRD as a kinetic approach during the different phases of treatment rather than as a static analysis.

We expected that the intensification of treatment—the administration of one dose of ibritumomab tiuxetan before RM—would contribute significantly to the efficacy of our response-adapted approach for non-CMR patients. The choice of using RIT in this group of patients was based on the combined findings of two randomized trials that showed the efficacy of consolidation of RIT after induction ICT[26] and also suggested the need for RM in this group of high-risk patients treated with RIT.[27] Unfortunately, we were not able to reach any conclusion on the efficacy of the planned intervention mainly because of the low number of treated patients. Indeed, one important result of the FOLL12 is the 90% CMR rate in our series, which was much higher than what was initially expected but in line with what other recent trials have reported.[2,28] Moreover, the observed poorer survival of non-CMR versus CMR patients confirmed that non-CMR patients are a high-risk group for whom more effective active therapeutic options are warranted.

On the basis of the above observations, the FOLL12 trial suggests that postinduction maintenance is appropriate for all responding patients. Our study, however, also confirms that even if treated with standard therapy, FL shows heterogenous outcomes. Treatment adaptation is thus a relevant clinical question to optimize treatment exposure, safety, and

costs, but caution should be used, as putative benefits may not compensate for an acceptable loss of efficacy, as shown in the present study.

For the small group of nonresponding high-risk patients, there is room to explore the activity of some of the new agents that are currently in clinical development. Among these, lenalidomide is currently being investigated in addition to maintenance rituximab therapy in PET+ FL patients in the PETREA trial by colleagues in the United Kingdom and Australia. More interestingly, novel bispecific agents and CART represent promising new options to overcoming the poor outcome of non-CMR high-risk patients in a response-adapted approach to patients with FL.

Conversely, for the larger group of patients with a low-risk profile, we believe that there is still room for treatment adaptation. As our results show, not administering RM in this group of patients increases their risk of lymphoma progression. Thus, we believe that a more promising strategy for patients with low-risk FL could be to act on the cytotoxic component of ICT, reducing it when not necessary.

In this scenario, the main aspect of treatment personalization is related to the choice of accurate predictors and to the combination of available prognostic factors to define accurate predictive models.

The FOLL12 study has some limitations. The first is related to the choice of the molecular technique used to conduct MRD analysis: BCL-2/IGH PCR, although standardized by the EuroMRD group,[29] is still characterized by a 40% rate of patients who cannot be assessed because of the unavailability of a MM. To overcome this issue, we managed patients without MMs only on the basis of PET results, although this practical choice might have affected the efficacy of the experimental strategy. This important issue of no marker cases might be managed in future trials by increasing the number of translocation cluster regions[30] or by moving to high throughput technology, which, however, have only offered very preliminary data in FL so far.[31–35]

As a second limitation, we acknowledge that a better assessment of a nonlifesaving therapy such as RM should integrate the evaluation of efficacy, safety, and patient-reported outcomes including quality of life that was lacking in our trial. Moreover, we also acknowledge that, as frequently observed in pure academic trials, there is a tendency to under-report safety events. However, this limitation does not affect the main study results, thanks also to the randomized design.

In conclusion, the FOLL12 study clearly shows that, although MR and MRD negativization are prognostic for PFS, the 2-year maintenance approach with R is clearly superior in different subgroups, especially in those defined at low risk of recurrence on the basis of PET and MRD response.

PRIOR PRESENTATION

Presented (in part) at the 15th International Conference on Malignant Lymphomas (ICML), Lugano, Switzerland, June 18-22, 2019 and 16th International Conference on Malignant Lymphomas (ICML), Lugano, Switzerland, June 18-22, 2021.

CLINICAL TRIAL INFORMATION

NCT02063685

UTHOR CONTRIBUTIONS

Conception and design: Stefano Luminari, Marco Ladetto, Massimo Federico

Administrative support: Martina Manni, Luigi Marcheselli, Alessandra Dondi
Provision of study materials or patients: Stefano Luminari, Martina Manni, Carola Boccomini, Lucia Farina, Jacopo Olivieri, Simone Ferrero, Luca Arcaini, Sofya Kovalchuk, Tetiana Skrypets, Francesca Ricci, Gloria Margiotta Casaluci, Anna Merli, Annalisa Arcari, Antonella Anastasia Collection and assembly of data: Stefano Luminari, Martina Manni, Alessandra Tucci, Carola Boccomini, Lucia Farina, Jacopo Olivieri, Luca Guerra, Simone Ferrero, Luca Arcaini, Federica Cavallo, Sofya Kovalchuk, Ilaria del Giudice, Stephane Chauvie, Caterina Patti, Caterina Stelitano, Francesca Ricci, Antonello Pinto, Gloria Margiotta Casaluci, Vittorio R. Zilioli, Anna Merli, Marco Ladetto, Silvia Bolis, Annalisa Chiarenza, Antonella Anastasia, Alessandra Dondi, Donato Mannina, Massimo Federico

Data analysis and interpretation: Stefano Luminari, Martina Manni, Sara Galimberti, Annibale Versari, Luigi Marcheselli, Simone Ferrero, Tetiana Skrypets, Ilaria del Giudice, Stephane Chauvie, Marco Ladetto, Annalisa Chiarenza, Annalisa Arcari

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

REFERENCES

1.   Hiddemann W, Barbui AM, Canales MA, et al: Immunochemotherapy with obinutuzumab or rituximab for previously untreated follicular lymphoma in the GALLIUM study: Influence of chemotherapy on efficacy and safety. J Clin Oncol 36:2395-2404, 2018

2.   Marcus R, Davies A, Ando K, et al: Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med 377:1331-1344, 2017

3.   Herold M, Scholz CW, Rothmann F, et al: Long-term follow-up of rituximab plus first-line mitoxantrone, chlorambucil, prednisolone and interferon-alpha as maintenance therapy in follicular lymphoma. J Cancer Res Clin Oncol 141:1689-1695, 2015

4.   Bachy E, Seymour JF, Feugier P, et al: Sustained progression-free survival benefit of rituximab maintenance in patients with follicular lymphoma: Long-term results of the PRIMA study. J Clin Oncol 37:2815-2824, 2019

5.   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 377:42-51, 2011

6.   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 36:689-696, 2018

7.   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 36:697-703, 2018

8.   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 33:2516-2522, 2015

9.   Luminari S, Biasoli I, Arcaini L, et al: The use of FDG-PET in the initial staging of 142 patients with follicular lymphoma: A retrospective study from the FOLL05 randomized trial of the Fondazione Italiana Linfomi. Ann Oncol 24:2108-2112, 2013

10.   Luminari S, Biasoli I, Versari A, et al: The prognostic role of post-induction FDG-PET in patients with follicular lymphoma: A subset analysis from the FOLL05 trial of the Fondazione Italiana Linfomi (FIL). Ann Oncol 25:442-447, 2014

11.   Barrington SF, Kirkwood AA, Franceschetto A, et al: PET-CT for staging and early response: Results from the response-adapted therapy in advanced Hodgkin lymphoma study. Blood 127:1531-1538, 2016

12.   Trotman J, Barrington SF, Belada D, et al: Prognostic value of end-of-induction PET response after first-line immunochemotherapy for follicular lymphoma (GALLIUM): Secondary analysis of a randomised, phase 3 trial. Lancet Oncol 19:1530-1542, 2018

13.   Delfau-Larue M-H, Boulland M-L, Beldi-Ferchiou A, et al: Lenalidomide/rituximab induces high molecular response in untreated follicular lymphoma: LYSA ancillary RELEVANCE study. Blood Adv 4:3217-3223, 2020

14.   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 99:856-862, 2002

15.   Ladetto M, Lobetti-Bodoni C, Mantoan B, et al: Persistence of minimal residual disease in bone marrow predicts outcome in follicular lymphomas treated with a

rituximab-intensive program. Blood 122:3759-3766, 2013

16.   Galimberti S, Luminari S, Ciabatti E, et al: Minimal residual disease after conventional treatment significantly impacts on progression-free survival of patients with follicular lymphoma: The FIL FOLL05 trial. Clin Cancer Res 20:6398-6405, 2014

17.   Pott C, Sehn LH, Belada D, et al: MRD response in relapsed/refractory FL after obinutuzumab plus bendamustine or bendamustine alone in the GADOLIN trial.

Leukemia 34:522-532, 2020

18.   Federico M, Mannina D, Versari A, et al: Response oriented maintenance therapy in advanced follicular lymphoma. Results of the interim analysis of the FOLL12 trial conducted by the Fondazione Italiana Linfomi. Hematol Oncol 37:153-154, 2019

19.   Swerdlow S, Campo E, Harris N, et al: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC Library, 2008

20.   Federico M, Bellei M, Marcheselli L, et al: Follicular Lymphoma International Prognostic Index 2: A new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol 27:4555-4562, 2009

21.   Cheson BD, Pfistner B, Juweid ME, et al: Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586, 2007

22.   Ferrero S, Monitillo L, Mantoan B, et al: Rituximab-based pre-emptive treatment of molecular relapse in follicular and mantle cell lymphoma. Ann Hematol 92:

1503-1511, 2013

23.   Trotman J, Luminari S, Boussetta S, et al: Prognostic value of PET-CT after first-line therapy in patients with follicular lymphoma: A pooled analysis of central scan review in three multicentre studies. Lancet Haematol 1:e17-e27, 2014

24.   Luminari S, Galimberti S, Versari A, et al: Positron emission tomography response and minimal residual disease impact on progression-free survival in patients with follicular

lymphoma. A subset analysis from the FOLL05 trial of the Fondazione Italiana Linfomi. Haematologica 101:e66-e68, 2016

25. Ladetto M, Magni M, Pagliano G, et al: Rituximab induces effective clearance of minimal residual disease in molecular relapses of mantle cell lymphoma. Biol

Blood Marrow Transplant 12:1270-1276, 2006

26. Morschhauser F, Radford J, Van Hoof A, et al: Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol 26:5156-5164, 2008

27. Lopez-Guillermo A, Canales MA, Dlouhy I, et al: A randomized phase II study comparing consolidation with a single dose of 90y ibritumomab tiuxetan (Zevalin®)

(Z) vs. maintenance with rituximab (R) for two years in patients with newly diagnosed follicular lymphoma (FL) responding to R-CHOP. Preliminary results at 36 months from randomization. Blood 122:369, 2013

28. Morschhauser F, Fowler NH, Feugier P, et al: Rituximab plus lenalidomide in advanced untreated follicular lymphoma. N Engl J Med 379:934-947, 2018

29. EuroMRD group: www.euromrd.org

30. Pott C, Bru¨ ggemann M, Ritgen M, et al: MRD detection in B-cell non-Hodgkin lymphomas using Ig gene rearrangements and chromosomal translocations as targets for real-time quantitative PCR. Methods Mol Biol 1956:199-228, 2019

31. Bru¨ ggemann M, Kotrova´ M, Knecht H, et al: Standardized next-generation sequencing of immunoglobulin and T-cell receptor gene recombinations for MRD marker identification in acute lymphoblastic leukaemia; a EuroClonality-NGS validation study. Leukemia 33:2241-2253, 2019

32. Cavalli M, De Novi LA, Della Starza I, et al: Comparative analysis between RQ-PCR and digital droplet PCR of BCL2/IGH gene rearrangement in the peripheral blood and bone marrow of early stage follicular lymphoma. Br J Haematol 177:588-596, 2017

33. Drandi D, Ferrero S, Ladetto M: Droplet digital PCR for minimal residual disease detection in mature lymphoproliferative disorders. Methods Mol Biol 1768: 229-256, 2018

34. Di Paolo A, Arrigoni E, Luci G, et al: Precision medicine in lymphoma by innovative instrumental platforms. Front Oncol 9:1417, 2019

35. Pott C, Knecht H, Herzog A, et al: Standardized IGH-based next-generation sequencing for MRD detection in follicular lymphoma. Blood 130:1491, 2017

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Response-Adapted Postinduction Strategy in Patients With Advanced-Stage Follicular Lymphoma: The FOLL12 Study

Stefano Luminari

Consulting or Advisory Role: Roche, Gilead Sciences, Celgene, Genmab, Regeneron, Incyte

Travel, Accommodations, Expenses: Janssen, Celgene

Sara Galimberti

Speakers' Bureau: Novartis Italy, Jazz Pharmaceuticals, Incyte, AbbVie Travel, Accommodations, Expenses: Jazz Pharmaceuticals, Janssen Oncology, Incyte, Novartis Italy

Annibale Versari

Consulting or Advisory Role: Novartis

Travel, Accommodations, Expenses: Novartis

Alessandra Tucci

Consulting or Advisory Role: Janssen, Takeda

Travel, Accommodations, Expenses: Sandoz

Luigi Marcheselli

Uncompensated Relationships: Sandoz SpA

Simone Ferrero

Consulting or Advisory Role: Janssen-Cilag, EUSA Pharma, Clinigen Group, Incyte

Speakers' Bureau: Janssen-Cilag, Servier, EUSA Pharma, Gentili

Research Funding: Gilead Sciences (Inst), MorphoSys (Inst), Janssen (Inst) Travel, Accommodations, Expenses: Roche, Servier, Sanofi, Janssen-Cilag, EUSA Pharma, Gentili

Luca Arcaini

Consulting or Advisory Role: Roche, Janssen-Cilag, Verastem, Incyte, EUSA Pharma, Celgene/Bristol Myers Squibb

Speakers' Bureau: EUSA Pharma

Research Funding: Gilead Sciences

Travel, Accommodations, Expenses: Roche, Celgene, Janssen-Cilag, EUSA Pharma

Federica Cavallo Honoraria: Servier

Consulting or Advisory Role: Gilead Sciences, Roche

Travel, Accommodations, Expenses: Celgene

Tetiana Skrypets Honoraria: Takeda

Ilaria del Giudice

Consulting or Advisory Role: Tolero Pharmaceuticals, AstraZeneca

Stephane Chauvie

Stock and Other Ownership Interests: Dixit

Honoraria: Sirtex Medical

Speakers' Bureau: TERUMO, Sirtex Medical

Research Funding: Roche

Antonello Pinto

Honoraria: Roche/Genentech, Merck Sharp & Dohme, Bristol Myers Squibb, Celgene, Servier, Incyte

Consulting or Advisory Role: Servier, Roche/Genentech, Merck, Takeda

Speakers' Bureau: Roche/Genentech

Marco Ladetto

Honoraria: AbbVie, Amgen, ADC Therapeutics, BeiGene, Celgene, Gentili, Kite/ Gilead, Novartis, Incyte, Janssen, Jazz Pharmaceuticals, Regeneron, Roche Consulting or Advisory Role: Jazz Pharmaceuticals, Roche, Janssen, Regeneron, Gilead Sciences, Novartis, Incyte

Speakers' Bureau: Incyte

Research Funding: ADC Therapeutics (Inst), Janssen (Inst)

Annalisa Chiarenza

Consulting or Advisory Role: Roche/Genentech

Annalisa Arcari

Consulting or Advisory Role: Janssen-Cilag

Travel, Accommodations, Expenses: Janssen-Cilag, Takeda

Massimo Federico

Consulting or Advisory Role: Takeda, Menarini, Erytech Pharma, Medivation
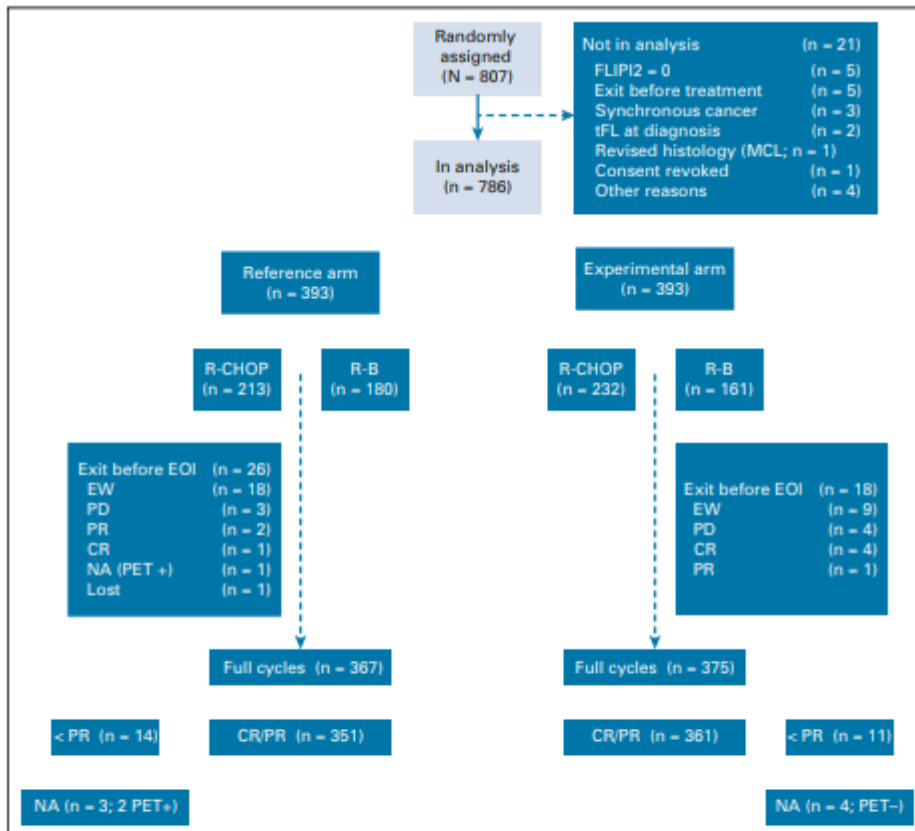
FIG 1. Treatment allocation and number of patients included in analysis, according to the CONSORT statement. Other reasons: 1 LFEV < 50%, 1 stage Ia, 1 PET−, and 1 HBV+. CR, complete remission; EOI, end of induction; EW, early withdrawal; FLIPI2, Follicular Lymphoma International Prognostic Index 2; tFL, transformed follicular lymphoma; HBV, hepatitis B virus; LFEV, left ventricular ejection fraction; MCL, mantle cell lymphoma; NA, not assessed; PD, progressive disease; PET, positron emission tomography; PR, partial remission; R-B, rituximab plus bendamustine; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

TABLE 1. Characteristics of Patients at Baseline and Response With Full Induction Treatment (n = 744)

Variable	Reference Arm No. (%)	Experimental Arm No. (%)	Total No. (%)
Age, years			
> 60	176 (48)	192 (51)	368 (49)
Sex			
Female	191 (52)	195 (52)	386 (52)
B2M			
> UNL	199 (54)	200 (53)	399 (54)
BM			
+	202 (55)	213 (57)	415 (56)
LoDLIN, cm			
> 6	203 (55)	212 (56)	415 (56)
Hemoglobin, g/dL			
< 12	61 (17)	49 (13)	110 (15)
Nodal sites			
> 4	157 (43)	146 (39)	303 (41)
Ann Arbor stage			
III-IV	324 (88)	335 (89)	659 (89)
LDH			
> UNL	79 (22)	81 (22)	160 (22)
FLIPI2			
1-2	221 (60)	227 (60)	448 (60)
3-5	147 (40)	149 (40)	296 (40)
FLIPI			
0-1	90 (25)	89 (24)	179 (25)
2	142 (40)	152 (42)	294 (41)
3-5	122 (34)	123 (34)	245 (34)
Response at EOI			
CR	601 (82)	300 (80)	301 (81)
PR	50 (14)	61 (16)	111 (15)
ORR	351 (96)	361 (96)	712 (96)

Abbreviations: B2M, beta-2-microglobulin; BM, bone marrow; CR, complete remission; EOI, end of induction; FLIPI2, Follicular Lymphoma International Prognostic Index 2; LDH, lactate dehydrogenase; LoDLIN, longest diameter of the largest involved node; ORR, overall response rate; PR, partial remission; UNL, upper normal level.
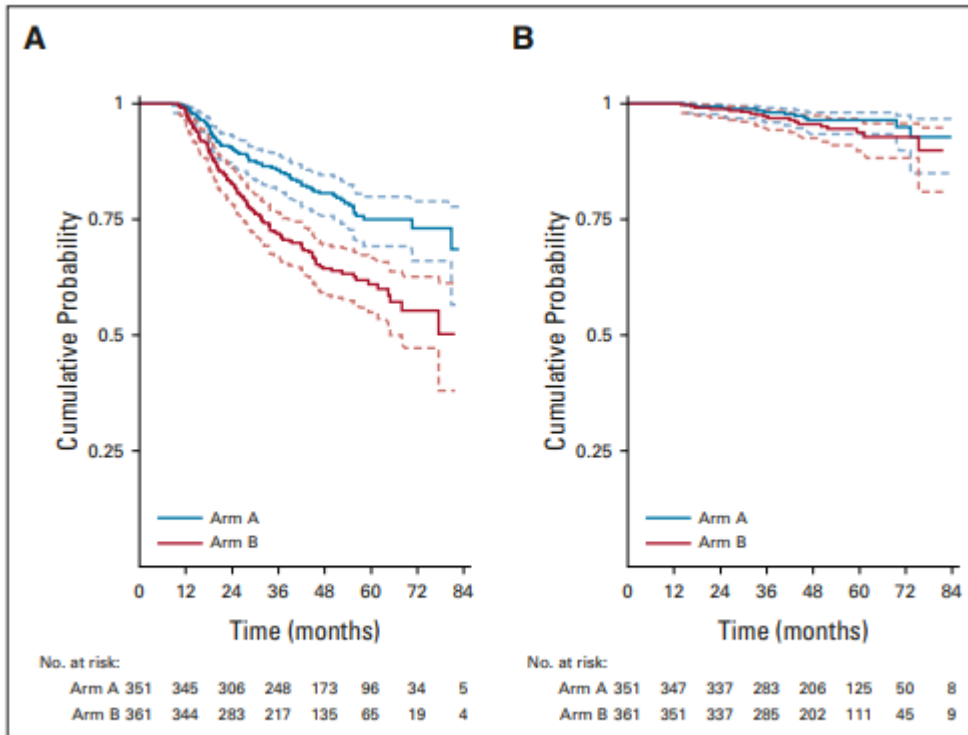
FIG 2. (A) PFS and (B) OS in the reference and experimental arms (n = 712). Arm A, reference arm; Arm B, experimental arm; OS, overall survival; PFS, progression-free survival.
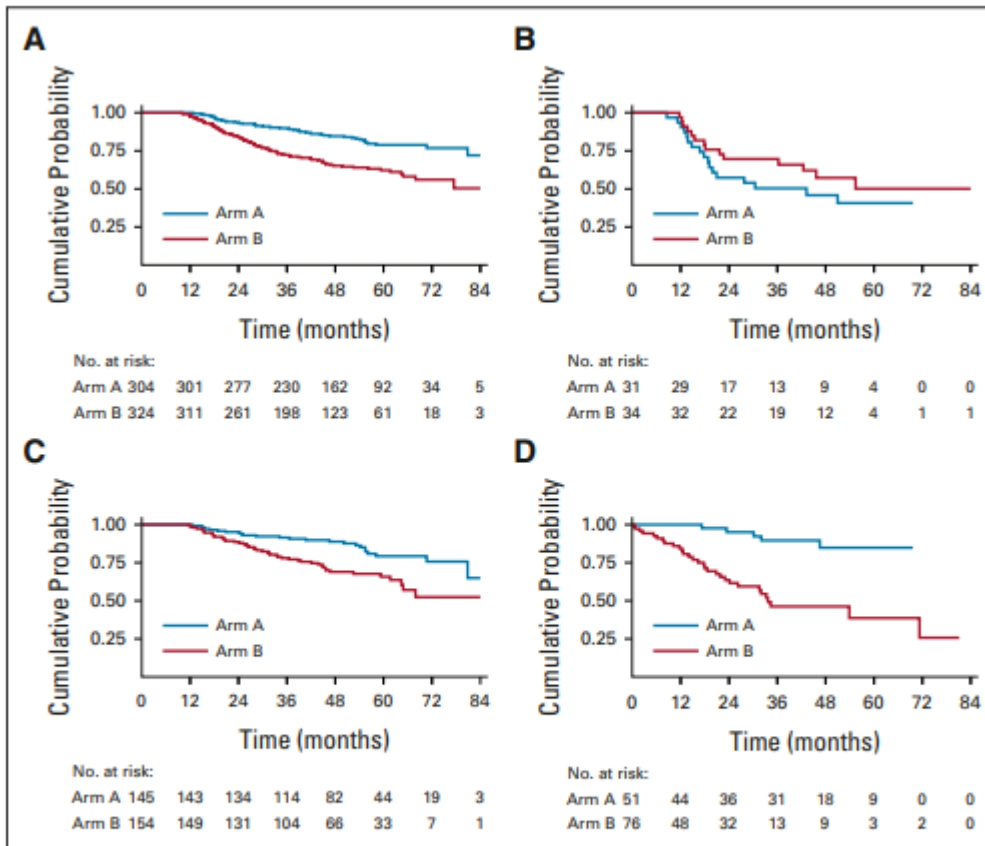
FIG 3. PFS for patients in CR/PR after EOI with reviewed PET and MRD: (A) EOT PET–, (B) EOT PET+, (C) EOT PET/MRD–/–, and (D) EOT PET– and MRD-positive at EOT or repositivized during follow-up. Arm A, reference arm; Arm B, experimental arm; CR, complete remission; EOI, end of induction; EOT, end of treatment; MRD, minimal residual disease; PET, positron emission tomography; PFS, progression-free survival; PR, partial remission.

Variable	No.	Fail	HR (95% CI)
Age, years			
< 60	365	96	2.21 (1.46 to 3.36)
≥ 60	347	101	1.66 (1.11 to 2.48)
Sex			
Male	337	103	2.03 (1.35 to 3.05)
Female	375	94	1.79 (1.18 to 2.71)
R-CHOP	413	123	1.68 (1.17 to 2.43)
R-B	299	74	2.37 (1.48 to 3.81)
FLIPI2			
1-2	437	94	1.91 (1.25 to 2.91)
3-5	275	103	2.02 (1.36 to 3.02)
Stage			
II	82	23	0.95 (0.42 to 2.17)
III-IV	629	174	2.13 (1.56 to 2.91)
NS			
≤ 4	416	101	1.83 (1.22 to 2.74)
> 4	288	95	1.97 (1.30 to 2.98)
FLIPI			
0-2	461	113	1.92 (1.31 to 2.81)
3-5	226	79	1.84 (1.16 to 2.91)

FIG 4. PFS with interaction terms (forest plot; n = 712). FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; NS, nodal sites; PFS, progression-free survival; R-B, rituximab plus bendamustine; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

TABLE 2. Hematologic and Extra-Hematologic Adverse Events With CTCAE > 2 During Maintenance or Follow-Up in Patients With PET– and Patients With PET+ by Arm

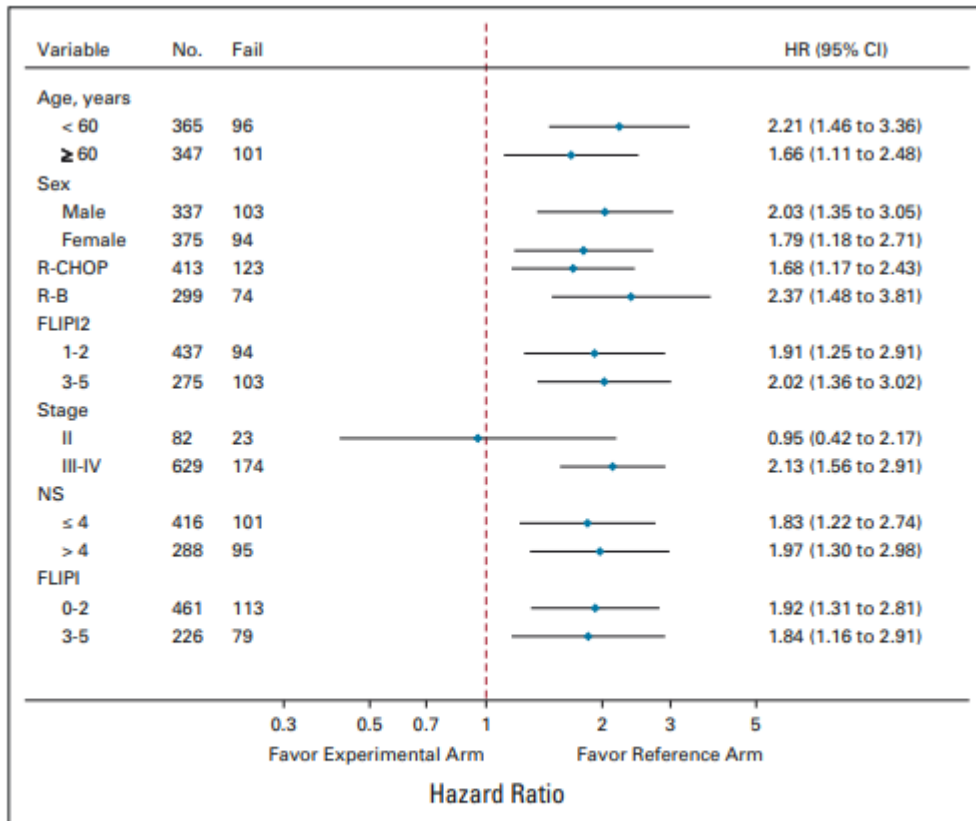**Adverse Events in Patients With PET– at EOI (A = 284 and B = 280)**

| Hematologic | Reference Arm, No. (%) | | Experimental Arm, No. (%) | | |
Adverse Event	Grade 1-2	Grade > 2	Grade 1-2	Grade > 2	Pᵃ
Anemia	13 (4.6)	2 (0.7)	3 (1.1)	1 (0.4)	1.00
Leukopenia	19 (6.7)	2 (0.7)	6 (2.1)	2 (0.7)	1.00
Neutropenia	15 (5.3)	37 (13.0)	2 (0.7)	10 (3.6)	< .001
Thrombocytopenia	6 (2.1)	1 (0.3)	5 (1.8)	0	1.00
Febrile neutropenia	0	0	0	0	—
Extra-Hematologic	**Reference Arm, No. (%)**		**Experimental Arm, No. (%)**		**Pᵃ**
Adverse Event	Grade 1-2	Grade > 2	Grade 1-2	Grade > 2	
Cardiac disorders	4 (1.4)	4 (1.4)	5 (1.8)	5 (1.8)	.750
Congenital and/or familial and/or genetic disorders	0	0	0	0	—
Ear and labyrinth disorders	6 (2.1)	0	2 (0.7)	0	—
Endocrine disorders	0	0	0	2 (0.7)	
Eye disorders	0	0	2 (0.7)	0	—
GI disorders	6 (2.1)	0	10 (3.6)	1 (0.4)	.496
General disorders	7 (2.5)	0	18 (6.4)	0	—
Hepatobiliary disorders	1 (0.3)	0	1 (0.4)	0	—
Immune system disorders	0	0	0	1 (0.4)	.496
Infections and infestations	10 (3.5)	1 (0.3)	9 (3.2)	4 (1.4)	.214
Injury and/or poisoning and/or procedural complications	0	0	0	0	—
Investigations	0	0	1 (1.4)	1 (0.4)	.496
Metabolism and nutrition disorders	2 (0.7)	0	1 (0.4)	0	—
Musculoskeletal and connective tissue disorders	1 (0.3)	1 (0.3)	10 (3.6)	0	1.00
Neoplasms benign and/or malignant and/or unspecified	3 (1.1)	1 (0.3)	2 (0.7)	4 (1.4)	.214
Nervous system disorders	6 (2.1)	0	8 (2.9)	2 (0.7)	.246
Pregnancy and/or puerperium and perinatal conditions	0	0	0	0	—
Psychiatric disorders	1 (0.3)	0	1 (0.4)	1 (0.4)	.496
Renal and urinary disorders	3 (1.1)	1 (0.3)	4 (1.4)	1 (0.4)	1.00
Reproductive system and breast disorders	1 (0.3)	0	1 (0.4)	1 (0.4)	.496
Respiratory or thoracic and mediastinal disorders	13 (4.6)	0	21 (7.5)	1 (0.4)	.496
Skin and subcutaneous tissue disorders	3 (1.1)	0	10 (3.6)	1 (0.4)	.496
Surgical and medical procedures	0	0	1 (0.4)	0	—
Vascular disorders	2 (0.7)	0	5 (1.8)	0	—
Others (specify)	9 (3.2)	1 (0.3)	11 (3.9)	2 (0.7)	.622

Adverse Events in Patients With PET+ at EOI (A = 30 and B = 32)

| Hematologic | Reference Arm, No. (%) | | Experimental Arm, No. (%) | | |
Adverse Event	Grade 1-2	Grade > 2	Grade 1-2	Grade > 2	Pᵃ
Anemia	1 (3.3)	0	5 (15.6)	2 (6.2)	.492
Leukopenia	1 (3.3)	0	2 (6.2)	3 (9.4)	.238
Neutropenia	0	3 (10.0)	2 (6.2)	14 (43.7)	.004

TABLE 2. Hematologic and Extra-Hematologic Adverse Events With CTCAE > 2 During Maintenance or Follow-Up in Patients With PET– and Patients With PET+ by Arm (continued)

Adverse Events in Patients With PET+ at EOI (A = 30 and B = 32)

| Hematologic | Reference Arm, No. (%) | | Experimental Arm, No. (%) | | |
Adverse Event	Grade 1-2	Grade > 2	Grade 1-2	Grade > 2	Pᵃ
Thrombocytopenia	0	0	4 (12.5)	12 (37.5)	< .001
Febrile neutropenia	1 (3.3)	0	0	0	—
Extra-Hematologic	**Reference Arm, No. (%)**		**Experimental Arm, No. (%)**		**Pᵃ**
Adverse Event	Grade 1-2	Grade > 2	Grade 1-2	Grade > 2	
GI disorders	2 (6.7)	3 (10.0)	1 (3)	0	.107
General disorders	1 (3.3)	0	3 (9.4)	0	—
Infections and infestations	0	0	2 (6.2)	0	—
Injury and/or poisoning and/or procedural complications	0	0	0	0	—
Musculoskeletal and connective tissue disorders	0	0	1 (3.1)	0	—
Neoplasms benign and/or malignant and/or unspecified	0	0	0	1 (3.1)	1.00
Nervous system disorders	0	1 (3.3)	0	0	.484
Respiratory or thoracic and mediastinal disorders	3 (10.0)	0	2 (6.2)	0	—
Skin and subcutaneous tissue disorders	1 (3.3)	0	3 (3.1)	0	—
Others (specify)	0	0	2 (6.2)	0	—

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; EOI, end of induction; PET, positron emission tomography.
ᵃFisher's exact test of frequency CTCAE grade > 2 between reference and experimental arms.

TABLE A1. List of FOLL12 Study Investigators

Principal Investigator	Site Location
Ladetto Marco	A.O. SS. Antonio e Biagio e Cesare Arrigo, S.C. Ematologia, Spalto Marengo 46—15121 Alessandria, Italy
Olivieri Attilio	AOU Ospedali Riuniti, Clinica di Ematologia, Via Conca 71—60126 Torrette, Ancona, Italy
Perrone Tommasina	AOU Policlinico Consorziale, U.O. Ematologia con Trapianto, Piazza Giulio Cesare 11—70124 Bari, Italy
Conconi Annarita	Ospedale Degli Infermi, S.C. Oncologia, Via dei Ponderanesi 2—13875 Ponderano, Biella, Italy
Stefoni Vittorio	Policlinico S.Orsola-Malpighi, Istituto di Ematologia "Seragnoli", Via Giuseppe Massarenti 9—40138 Bologna, Italy
Tucci Antonella	ASST Spedali Civili di Brescia, Ematologia, Piazzale Spedali Civili 1—25123 Brescia, Italy
Pastore Domenico	Ospedale Antonio Perrino, U.O. Ematologia e Trapianti di Midollo, Str. per lo Spada 5—72100 Brindisi, Italy
Usai Sara Veronica	Ospedale Businco, SC Ematologia e CTMO, Via Edward Jenner 1—09121 Cagliari, Italy
Aglietta Massimo	Fondazione del Piemonte per l'Oncologia—IRCCS, Ematologia, SP142 km 3,95, 10060 Candiolo, Torino, Italy
Chiarenza Annalisa	AOU Policlinico—Vittorio Emanuele Presidio Ospedale Ferrarotto, Ematologia, Via Salvatore Citelli 6—95123 Catania, Italy
Centurioni Riccardo	Azienda Sanitaria Unica Regionale 8, Medicina Interna e Ematologia, Via Ginevri, Contrada S. Domenico 1—62012 Civitanova Marche, Italy
Castellino Claudia	A.O. S. Croce e Carle, S.C. di Ematologia e Trapianto di Midollo Osseo, Via Antonio Carle 5—12100 Cuneo, Italy
Kovalchuk Sofya	Azienda Ospedaliera Universitaria Careggi, Unità funzionale di Ematologia, Largo Piero Palagi 1—50139 Firenze, Italy
Ballerini Filippo	Ospedale Policlinico San Martino S.S.R.L.—IRCCS per l'Oncologia, U.O. Clinica Ematologica, Largo Rosanna Benzi 10—16132 Genova, Italy
Ghiggi Chiara	Ospedale Policlinico San Martino S.S.R.L.—IRCCS per l'Oncologia, Ematologia, Largo Rosanna Benzi 10—16132 Genova, Italy
Di Renzo Nicola	Ospedale Vito Fazzi, Ematologia, Piazza Filippo Muratore 1—73100 Lecce, Italy
Fragasso Alberto	Ospedale Madonna delle Grazie, Ematologia, Contrada Cattedra Ambulante, 75100 Matera. Italy

TABLE A1. List of FOLL12 Study Investigators (continued)

Principal Investigator	Site Location
Ronconi Sonia	IRCCS Istituto Romagnolo per lo studio dei Tumori "Dino Amadori"—IRST S.R.L., Ematologia, Via Piero Maroncelli 40—47014 Meldola, Italy
Mannina Donato	Azienda Ospedali Riuniti Papardo-Piemonte, S.C. Ematologia, Contrada Papardo, 98158 Messina, Italy
Baldini Luca	Ospedale Maggiore Policlinico—Fondazione IRCCS Ca' Granda, Ematologia, Via della Commenda 10—20122 Milano, Italy
Lucia Farina	Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Ematologia, Via Giacomo Venezian 1—20133 Milano, Italy
Zilioli Vittorio Ruggero	ASST Grande Ospedale Metropolitano Niguarda, SC Ematologia, Piazza dell'Ospedale Maggiore 3—20162 Milano. Italy
Bari Alessia	Azienda Ospedaliero-Universitaria Policlinico di Modena, Dipartimento di Scienze Mediche e Chirurgiche Materno-Infantili e dell'Adulto, Via del Pozzo 71—41124 Modena, Italy
Bolis Silvia	ASST MONZA Ospedale S. Gerardo, Ematologia, Via G. B. Pergolesi 33—20900 Monza, Italy
Pinto Antonio	Istituto Nazionale Tumori—IRCCS Fondazione G. Pascale, UOC Ematologia Oncologica, Via Mariano Semmola 53—80131 Napoli, Italy
Margiotta Casaluci Gloria	AOU Maggiore della Carità di Novara, SCDU Ematologia, Corso Giuseppe Mazzini 18—28100 Novara, Italy
Doa Gianluca	P.O. San Francesco, U.O.C. Ematologia e CTMO, Via Salvatore Mannironi, 08100 Nuoro, Italy
Califano Catello	Presidio ospedaliero "A. TORTORA", U.O. Onco-ematologia, Via Alcide de Gasperi 59—84016 Pagani, Italy
Mancuso Salvatrice	AOU Policlinico Giaccone, Ematologia, Via del Vespro 129—90127 Palermo, Italy
Patti Caterina	A.O. Ospedali Riuniti Villa Sofia-Cervello, Divisione di Ematologia, Viale Strasburgo 233—90146 Palermo, Italy
Re Francesca	AOU di Parma, UO Ematologia e CTMO, Viale Antonio Gramsci 14—43126 Parma, Italy
Arcaini Luca	IRCCS Policlinico S. Matteo di Pavia, Div. di Ematologia, Viale Camillo Golgi 19—27100 Pavia, Italy
Falini Brunangelo	Ospedale S. Maria della Misericordia, Ematologia, Piazzale Giorgio Menghini 1—06129 Perugia, Italy

TABLE A1. List of FOLL12 Study Investigators (continued)

Principal Investigator	Site Location
Angrilli Francesco	P.O. Spirito Santo di Pescara, UOS Dipartimentale—Centro di diagnosi e Terapia dei linfomi, Via Fonte Romana 8—65124 Pescara, Italy
Arcari Annalisa	Ospedale Guglielmo da Saliceto, U.O.Ematologia, Via Taverna Giuseppe 49—29121 Piacenza, Italy
Sara Galimberti	AOU Pisana, U.O. Ematologia, Via Roma 67—56126 Pisa, Italy
Stelitano Caterina	Grande Ospedale Metropolitano Bianchi Melacrino Morelli, Ematologia, Via Giuseppe Melacrino 21—89124 Reggio Calabria, Italy
Merli Anna	Ospedale degli Infermi di Rimini, U.O. di Ematologia, Viale Luigi Settembrini 2—47923 Rimini, Italy
Pietrantuono Giuseppe	IRCCS-Centro di Riferimento Oncologico, UO di ematologia e Trapianto Cellule Staminali, Via Padre Pio 1—85028 Rionero In Vulture PZ, Italy
Pulsoni Alessandro	Policlinico Umberto I—Università "La Sapienza", Istituto Ematologia -Dipartimento di Medicina Traslazionale e di Precisione, Viale del Policlinico 155—00161 Roma, Italy
Francesca Ricci	Istituto Clinico Humanitas, U.O. Ematologia, Via Alessandro Manzoni 56—20089 Rozzano MI, Italy
Cascavilla Nicola	Casa Sollievo della Sofferenza, U.O. Ematologia, Viale Cappuccini 1—71013 San Giovanni Rotondo FG, Italy
Fabbri Alberto	AOU Senese, U.O.C. Ematologia, V.le Mario Bracci 16—53100 Siena, Italy
Liberati Anna Marina	A.O. S. Maria di Terni, S.C. Oncoematologia, Viale Tristano di Joannuccio—05100 Terni, Italy
Boccomini Carola	A.O.U. Città della Salute e della Scienza di Torino, S.C.Ematologia, Corso Bramante 88 10126 Torino, Italy
Cavallo Federica	A.O.U. Città della Salute e della Scienza di Torino, Ematologia Universitaria, Corso Bramante 88—10126 Torino, Italy
Stefani Piero Maria	Ospedale Ca' Foncello, S.C di Ematologia, Piazzale Ospedale 1—31100 Treviso, Italy
Pavone Vincenzo	A.O. C. Panico, U.O.C Ematologia e Trapianto, Via San Pio X 4—73039 Tricase LE, Italy
Olivieri Jacopo	Azienda Sanitaria Universitaria Friuli Centrale (ASU FC), SOC Clinica Ematologica, Via Pozzuolo 330—33100 Udine, Italy
Passamonti Francesco	Ospedale di Circolo, U.O.C Ematologia, Via Lazio 36—21100 Varese, Italy