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ORIGINAL ARTICLE

Radioimmunotherapy versus autologous hematopoietic stem cell transplantation in relapsed/refractory follicular lymphoma: a Fondazione Italiana Linfomi multicenter, randomized, phase III trial

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Background: Optimal consolidation for young patilents with relapsed/refractory (R/R) follicular lymphoma (FL) remains uncertain in the rituximab era, with an unclear benefit of autologous stem cell transplantation (ASCT). The multicenter, randomized, phase III FLAZ12 (NCT01827605) trial compared anti-CD20 radioimmunotherapy (RIT) with ASCT as consolidation after chemoimmunotherapy, both followed by rituximab maintenance.

Patients and methods: Patients (age 18-65 years) with R/R FL and without significant comorbidities were enrolled and treated with three courses of conventional, investigator-chosen chemoimmunotherapies. Those experiencing at least a partial response were randomized 1 : 1 to ASCT or RIT before CD34+ collection, and all received postconsolidation rituximab maintenance. Progression-free survival (PFS) was the primary endpoint. The target sample size was 210 (105/group).

Results: Between August 2012 and September 2019, of 164 screened patients, 159 were enrolled [median age 57 (interquartile range 49-62) years, 55% male, 57% stage IV, 20% bulky disease]. The study was closed prematurely because of low accrual. Data were analyzed on 8 June 2023, on an intention-to-treat basis, with a 77-month median follow-up from enrollment. Of the 141 patients (89%), 70 were randomized to ASCT and 71 to RIT. The estimated 3-year PFS in both groups was 62% (hazard ratio 1.11, 95% confidence interval 0.69-1.80, $P = 0.6662$). The 3-year overall survival also was similar between the two groups. Rates of grade $\geq$3 hematological toxicity were 94% with ASCT versus 46% with RIT ($P < 0.001$), and grade $\geq$3 neutropenia occurred in 94% versus 41%, respectively ($P < 0.001$). Second cancers occurred in nine patients after ASCT and three after radioimmunotherapy ($P = 0.189$).

Conclusions: Even if prematurely discontinued, our study did not demonstrate the superiority of ASCT versus RIT. ASCT was more toxic and demanding for patients and health services. Both strategies yielded similar, favorable long-term outcomes, suggesting that consolidation programs milder than ASCT require further investigation in R/R FL.

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Key words: autologous hematopoietic stem cell transplantation, consolidation, follicular lymphoma, radioimmunotherapy, hematological toxicities, phase III trial

INTRODUCTION

Follicular lymphoma (FL), the second most common non-Hodgkin's lymphoma subtype in Western countries,[1] is characterized by BCL-2 overexpression, most often because of the IGH/BCL2 translocation (14;18) (q32; q21).[2] Its natural history typically involves an indolent clinical course and good responsiveness to first-line treatment.[2,3]

Although the introduction of rituximab either alone or in combination with chemotherapy has significantly improved outcomes with FL,[4-13] most patients still experience clinical relapse. Relapsed FL tends to respond to second-line treatment, but further remissions are shorter, and a substantial proportion of patients ultimately die of the disease or treatment-related toxicity. There is a lack of consensus on second-line treatment for patients with relapsed/refractory (R/R) FL, particularly those aged <65 years, and no chemotherapeutic program among those available in the European Union has proved superior over others.[14] To increase the complete remission (CR) rate and disease-free survival after salvage treatment, several guidelines still suggest consolidation with high-dose chemotherapy and autologous stem cell transplantation (ASCT).[15] This guidance is based mainly on the results of the CUP trial, which was conducted in the pre-rituximab era.[16] No compelling evidence of an ASCT benefit is available in the context of modern chemoimmunotherapy, particularly when followed by rituximab maintenance,[17] although some retrospective evidence suggests a potential advantage.[18] Radioimmunotherapy is an active agent in R/R FL.[19] As consolidation, it has been investigated after CHOP at diagnosis but is often used in the R/R setting as a less toxic consolidation regimen than ASCT.[20,21]

To address some of these unresolved issues, the Fondazione Italiana Linfomi (FIL) designed and conducted the randomized phase III FIL FLAZ-12 trial (ClinicalTrials.gov NCT01827605) to compare ASCT and radioimmunotherapy, two widely used consolidation regimens, in patients with R/R FL who experienced an objective response to conventional, routinely used chemoimmunotherapy. Treatment in both groups was completed with rituximab maintenance. Here, we report safety and efficacy data at a median follow-up of 77 months from enrollment.

METHODS

Study design and participants

A detailed description and schema of the trial are available in Supplementary Material S1, available at https://doi.org/10.1016/j.annonc.2023.10.095. Eligible patients had grade I–IIIa FL (according to the World Health Organization 2008 classification),[22] with age 18-65 years, Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (excepting lymphoma-related impairment of performance status), clinical indication for systemic treatment (i.e. stage II-IV disease requiring therapy according to the Italian Society of Hematology[23] and Groupe d'Etude des Lymphomes Folliculaires criteria[24]), and relapsed or refractory disease after two or fewer chemotherapy lines at least one containing rituximab. Patients receiving rituximab monotherapy as a unique treatment line were not eligible. Although rituximab maintenance was not considered a therapeutic line, prior treatment should have included rituximab. Progression of disease within 24 months (POD24) was assessed retrospectively. The diagnosis was based on the local pathology report, and tumor rebiopsy before study entry was mandatory only in case of suspected transformation (e.g. elevated serum lactate dehydrogenase or bulky mass). Additional eligibility criteria are provided in Supplementary Material S1, available at https://doi.org/10.1016/j.annonc.2023.10.095. Following confirmation of eligibility, patients started treatment.

Procedures

After an optional prephase with vincristine and steroids [intravenous vincristine 1.4 mg/m^2 on day 1, oral prednisone 100 mg (total dose) on days 1-5], patients were administered, as induction treatment, three courses of standard-dose immunochemotherapy at physician's discretion and based on prior therapy received as first- or second-line treatment. Potential choices were R-CHOP, R-DHAP, R-FM, R-ICE, R-IEV, or R-Bendamustine. For further information, see Supplementary Material S1, available at https://doi.org/10.1016/j.annonc.2023.10.095.

At the end of induction, the response was assessed by computed tomography according to the 2007 International Working Group Criteria for nonpositron emission tomography (PET)-avid lymphomas.[25] Patients experiencing CR or partial remission (PR) underwent 1 : 1 randomization to ASCT or radioimmunotherapy. The treatment arm was revealed only at the end of the mobilization procedure to ensure appropriate collection in the radioimmunotherapy arm for salvage purposes. Additional information is provided in Supplementary Material S1, Figure S1, available at https://doi.org/10.1016/j.annonc.2023.10.095.

All randomized patients underwent stem cell mobilization with rituximab–high-dose cytarabine. CD34+ peripheral blood stem cells were harvested by local procedures and at least 6 $\times$ 10^6 CD34+ cells/kg were required. After the mobilization response assessment, treatment was unblinded. Patients experiencing PR/CR in the ASCT arm but with a collection of <2 $\times$ 10^6 CD34+ cells/kg did not undergo ASCT and proceeded directly to rituximab maintenance. Patients in the radioimmunotherapy arm with inadequate platelet counts (<100,000/mm^3) and bone marrow clearance (infiltration >25% at the restaging pre-consolidation) proceeded directly to maintenance. All other

patients[25] with PR or CR[25] proceeded to the respective consolidation procedures (ASCT or radioimmunotherapy). Consolidation was started at least >6 weeks after peripheral blood stem cell collection.

Patients randomized to ASCT underwent conditioning with BEAM (BCNU, etoposide, cytarabine, melphalan) or FEAM (fotemustine, etoposide, cytarabine, melphalan). The TEAM conditioning regimen (thiotepa, etoposide, cytarabine, melphalan) was also allowed. For further information, see Supplementary Material S1, available at https://doi.org/10.1016/j.annonc.2023.10.095.

Patients randomized to radioimmunotherapy received intravenous rituximab 250 mg/m^2 on days 1 and 8. Immediately after the second rituximab infusion (day 8, range 7-9), they were administered ^{90}Y-ibritumomab tiuxetan (0.4 mCi/kg if platelets ≥150,000/mm^3, 0.3 mCi/kg if platelets 100,000 to <150,000/mm^3). ^{90}Y-ibritumomab tiuxetan was delivered as per indication. Following response assessment, patients experiencing CR/PR with adequate hematological recovery (absolute neutrophil count $>1.5 \times 10^6$ cells/L and platelets $>60 \times 10^6$ cells/L) within a maximum of 90 days after consolidation started rituximab maintenance for eight courses. If toxic effects developed, treatment was discontinued or modified as described in Supplementary Material S1, available at https://doi.org/10.1016/j.annonc.2023.10.095.

Neutropenia prophylaxis with granulocyte colony-stimulating factor was required every cycle per local practices. Growth factor prophylaxis was recommended, and blood product transfusions were allowed in accordance with the American Society of Clinical Oncology/European Society for Medical Oncology guidelines.[26,27] Additional prophylactic recommendations are detailed in Supplementary Material S1, available at https://doi.org/10.1016/j.annonc.2023.10.095.

This study was conducted according to the principles of the Declaration of Helsinki and in adherence with good clinical practice standards. All patients gave written informed consent. The final version of the protocol was reviewed and approved by the independent ethics committees of all participating centers.

Randomization and masking

Patients experiencing at least PR (according to Cheson et al.[25]) were stratified by enrolling center characteristics (carrying out ASCT and radioimmunotherapy locally, carrying out exclusively ASCT locally, not carrying out ASCT locally) and clinical response (PR or CR) after induction and then randomized 1 : 1 to ASCT or radioimmunotherapy. The web-based randomization procedure was continuously accessible (24 hours/day). The treatment arm was concealed from the treating physician until the completion of the mobilization phase (Supplementary Material S1, available at https://doi.org/10.1016/j.annonc.2023.10.095).

Assessments

Response to therapy was assessed locally according to the 2007 Revised Criteria for Malignant Lymphoma for non-PET-avid disorders.[25] The response was assessed by computed tomography and evaluation of laboratory or clinical data. PET was not mandatory and was not used for response assessment, as established by response criteria.[24]

Outcomes

For the primary efficacy analysis, the intention-to-treat (ITT) population included all randomly assigned patients regardless of receipt of the mobilization phase. The primary endpoint was progression-free survival (PFS), measured from the date of randomization to progression, relapse, or death from any cause, according to the 2007 Revised Criteria for Malignant Lymphoma for non-PET-avid disorders.[25] Secondary endpoints were overall survival (OS), event-free survival (EFS), treatment-free survival (TFS), overall response rate (ORR), CR rate,[25] and safety (Supplementary Material S1, available at https://doi.org/10.1016/j.annonc.2023.10.095). Additional secondary endpoints were minimal residual disease, within-arm rate of minimal residual disease conversion, and molecular relapse (Supplementary Material S1, available at https://doi.org/10.1016/j.annonc.2023.10.095) that will be presented in a separate manuscript.

The safety population included all patients receiving at least one dose of any study treatment. The frequency and severity of adverse events (AEs) were recorded based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. AEs were assessed during follow-up visits or when otherwise notified.

Statistical analysis

The 3-year PFS with radioimmunotherapy consolidation was expected to be 40%.[19] According to the O'Brien and Fleming group sequential design with a maximum of two stages, a total of 210 randomized patients (105 per group) was required (including a 5% precautionary increase in sample size) to detect an increase in 3-year PFS from 40% to 60% [hazard ratio (HR) 0.56] in the ASCT group, assessed with a two-sided log-rank test with α of 5% and a power of 85%. According to the literature, ∼80% of enrolled patients were expected to experience CR or PR after induction. Therefore an enrollment of 265 patients was required to randomize the estimated needed number of patients.

Because of lower-than-expected accrual, a protocol amendment in February 2014 increased the enrollment period. Despite this prolongation, however, the rate of patient registration was lower than expected, prompting the sponsor to discontinue enrollment on October 18, 2019. At that time, 164 patients were enrolled, and 138 had been randomized. Protocol procedures were continued as previously described. Further details are provided in Supplementary Material S1, available at https://doi.org/10.1016/j.annonc.2023.10.095.

Statistical analyses were conducted in the enrolled population (all patients enrolled in the study), the induction treatment population (all enrolled patients who started induction), the ITT population (all patients randomly assigned to radioimmunotherapy or ASCT), and the safety

population (all patients who received at least one dose of the assigned treatment). Time-to-event efficacy endpoints (PFS, OS, EFS, treatment-free survival) were estimated by the Kaplan—Meier method starting from the date of enrollment in the enrolled population and the date of randomization in the ITT population. Differences between groups were assessed in the ITT population by stratified log-rank test according to stratified randomization. HRs were estimated with the stratified Cox model. Subgroup analyses were carried out using the Cox model with adjustments for the stratification variables. The presence of interaction was tested by including an interaction term between the randomized group and the subgroup covariate of interest. The cumulative incidence of secondary malignancies was estimated using the method proposed by Gooley and colleagues.[28] Death without secondary malignancy was defined as a competing event, and comparisons between groups were made using the Fine and Gray model. Fisher's exact test was used to compare the proportion of patients between groups who experienced grade 3-4 toxic effects, with the *P* value calculated by doubling the probability. See Supplementary Material S1, available at https://doi.org/10.1016/j.annonc.2023.10.095 for more details about the statistical analysis plan. This study was registered with EudraCT (2012-000251-14) and ClinicalTrials.gov (NCT01827605).

RESULTS

Patients and treatment

From 30 August 2012 to 19 September 2019, a total of 164 patients were screened for inclusion (Figure 1). As noted, due to low enrollment, the sponsor, in accordance with the steering committee, decided to close enrollment on October 18, 2019 before, reaching the planned number of patients (Supplementary Material S1, available at https://doi.org/10.1016/j.annonc.2023.10.095). Neither the members of the FIL executive board nor the primary investigators had access to the clinical results by arm when the decision was made.

Of 164 patients, five patients were screened out (one unconfirmed diagnosis, two not needing treatment nor in overt relapse, one not previously treated with rituximab, and one without adequate cardiac function), and the remaining 159 were enrolled.

The clinical baseline characteristics of enrolled patients are presented in Table 1. The median age was 57 years (interquartile range 49-62), and 87 (55%) were male. Tumor rebiopsy was not mandatory but was nevertheless carried out before or after the start of screening in 126 (79%) patients, confirming FL histology in 125 (99%).

A total of 157 (99%) patients started treatment (one was excluded because of a high-grade histology rebiopsy). Of these 157 patients, 84 (53%) received R-Bendamustine, 60 (38%) R-DHAP, 7 (5%) R-CHOP, and 6 (4%) R-ICE. Treatment was stopped during induction or after restaging in 16 (10%) patients because of progression or stable disease ($n = 10$, 6%) and other causes [$n = 6$, 4%: three AEs (one renal, one cardiovascular, and one secondary tumor), one study withdrawal, and two poor compliance].

After induction, 141 (89%) patients experienced a clinical response (52 CR and 89 PR), meeting the eligibility criteria for randomization (Figure 1). Baseline demographics were similar between the two arms (Table 1). Of these 141 randomized patients, 70 were assigned to ASCT and 71 to radioimmunotherapy.

In the ASCT arm, 3 (2%) of 70 were not mobilized because of two hematological AEs and one withdrawal of consent, whereas in the radioimmunotherapy arm, all patients underwent the mobilization treatment. For two patients in the ASCT arm, adequate peripheral blood stem cell amounts could not be collected, and these patients were moved directly to rituximab maintenance as per protocol.

After mobilization, in the ASCT arm, 6 (16%) of 70 patients did not undergo ASCT despite successful mobilization (three progressive disease/relapses, one hematological AE, one withdrawal from treatment, and one medical decision), and 57 received ASCT (81.4%). In the radioimmunotherapy arm, 8 (11.2%) patients did not start the study drug (four progressive disease/relapses, two local unexpected logistic difficulties in carrying out radioimmunotherapy, one hematological AE, one poor adherence) and 63 (89%) received radioimmunotherapy. Of these, 11 were referred to a different center for radioimmunotherapy as prespecified in the protocol for centers without an adequate facility for this treatment.

In the ASCT arm, seven (11%) patients did not start maintenance (five AEs: two infective complications, two hematological, one cardiological, one progressive disease, and one medical decision). Fifty-four (77%) started rituximab maintenance, and 24 (34%) patients discontinued treatment [one toxic death, 12 relapses, seven AEs (four hematological and three infective), three medical decisions, and one lost to follow-up]. In the radioimmunotherapy arm, 58 of 71 (82%) patients started maintenance, and 5 did not (three progressive disease and two hematological AEs). Of those randomized to radioimmunotherapy, 23 (32%) did not complete maintenance [14 progressive disease/relapse, six AEs (three infective complications, one pulmonary, one hematological, one muscular pain), one poor adherence, one medical decision, and one severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection].

Efficacy

ORR. At the end of induction or at study discontinuation for those not completing treatment because of toxic effects or withdrawal, clinical response occurred in 145/159 (ORR 91%) patients, with CR in 52 (33%) and PR in 93 (58%). Ten (6%) patients had disease progression or stable disease. After consolidation, response occurred in 113 of 141 [ORR 80%, 95% confidence interval (CI) 73% to 86%]. Of these, 54 (77%, 95% CI 66% to 86%) were in the ASCT arm [CR in 48 (69%) and PR in 6 (9%)] and 59 (83%, 95% CI 72% to 91%) in the radioimmunotherapy arm [CR in 43 (61%) and PR in 16 (22%)], for a stratified odds ratio of 0.69 (95% CI 0.31-1.56, $P = 0.366$). Conversion from PR to CR occurred in 25 of 41 (61%) in the ASCT group versus 23 of 48 (48%) in the radioimmunotherapy group (stratified odds ratio 1.70, 95% CI 0.72-4.03, $P = 0.233$).

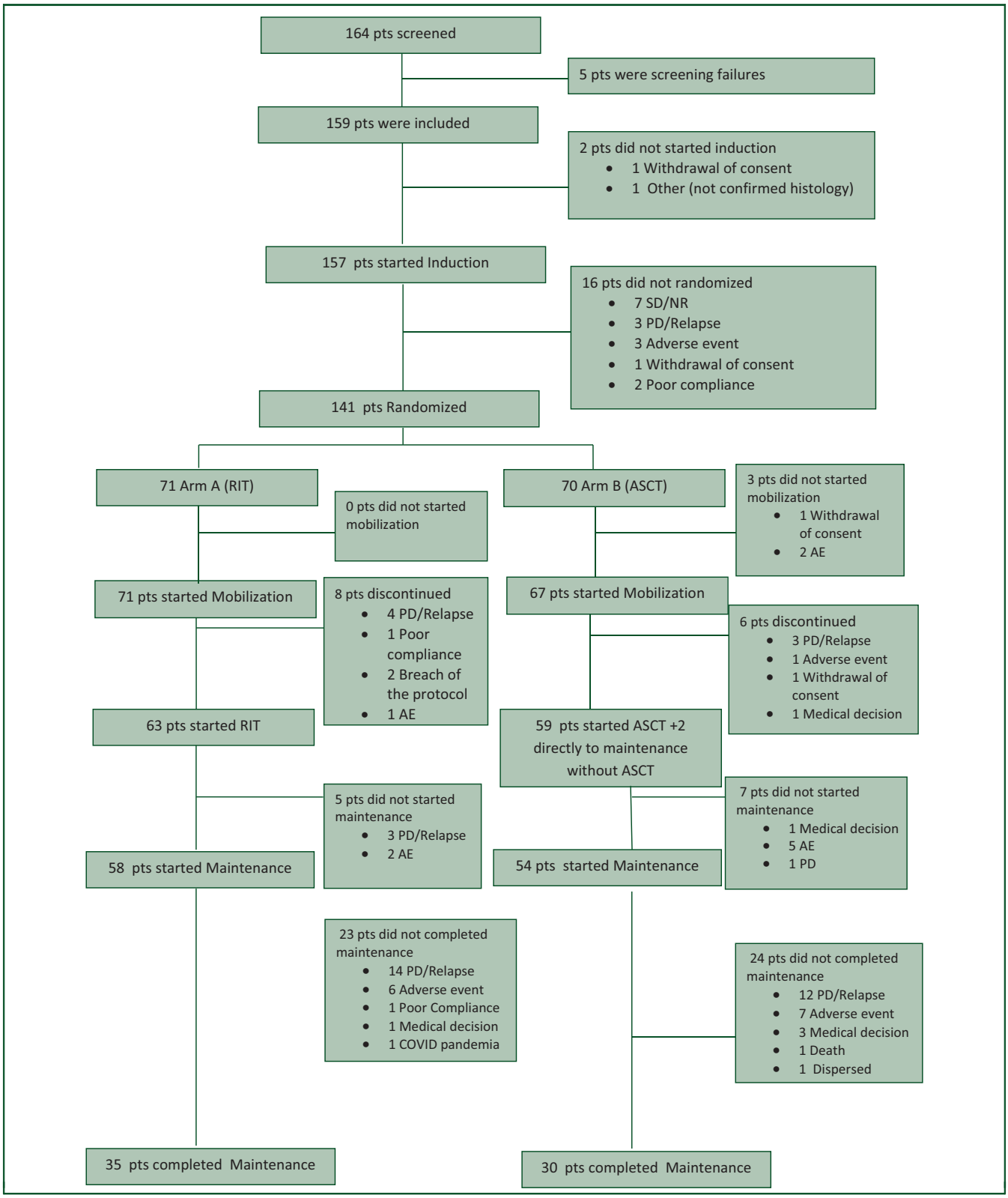

Figure 1. CONSORT diagram.
AE, adverse event; COVID-19, coronavirus disease 2019; PD, RIT, radioimmunotherapy.

PFS. Data were analyzed on an ITT basis on June 8, 2023 with a median follow-up of 77 months (interquartile range 50-100) from enrollment and 77 months (interquartile range 49-96) from randomization. For the enrolled population, the median PFS was 57 months (95% CI 38-85) with 3- and 6-year PFS of 60% (95% CI 52% to 67%) and 44% (95% CI 36% to 53%), respectively. The PFS of the entire population is shown in Supplementary Material S1, Figure S2, available at https://doi.org/10.1016/j.annonc.2023.10.095.

Table 1. Baseline patients and disease characteristics of all population

Characteristics		Enrolled (n = 159)	Nonrandomized (n = 18)	Randomized (n = 141)	Radioimmunotherapy (n = 71)	Autologous stem cell transplantation (n = 70)
Median age, years (range)		57 (50-62)	57 (51-62)	57 (48-62)	56 (49-62)	58 (48-62)
Male sex		87 (55)	10 (56)	77 (55)	41 (58)	36 (51)
Rebiopsy carried out at enrollment		126 (79)	12 (67)	114 (81)	58 (82)	56 (80)
Histology[a]	Follicular lymphoma G1	33 (21)	6 (33)	27 (19)	17 (24)	10 (14)
	Follicular lymphoma G2	84 (53)	8 (44)	76 (53)	34 (48)	42 (60)
	Follicular lymphoma G3a	42 (26)	4 (22)	38 (27)	20 (28)	18 (26)
Ann Arbor stage[b]	III	35 (22)	2 (11)	33 (23)	22 (31)	11 (16)
	IV	91 (57)	12 (67)	79 (56)	31 (44)	48 (69)
Systemic symptoms[b]	A	136 (86)	15 (83)	121 (86)	61 (86)	60 (86)
	B	23 (15)	3 (17)	20 (14)	10 (14)	10 (14)
Bone marrow involvement[b]		52 (33)	3 (17)	49 (35)	18 (25)	31 (44)
	Not available	14 (9)	4 (22)	10 (7)	6 (8)	4 (6)
Extranodal sites[b]	At least one positive	51 (32)	6 (33)	45 (32)	19 (27)	26 (37)
High lactate dehydrogenase > upper limit of normal[b]		36 (23)	4 (22)	32 (23)	18 (25)	14 (20)
Bulky disease ≥7 cm[b]		128 (80)	14 (78)	114 (81)	56 (79)	58 (83)
Eastern Cooperative Oncology Group performance status[b]	0	129 (81)	14 (78)	115 (82)	59 (83)	56 (80)
	1	26 (16)	3 (17)	23 (16)	10 (14)	13 (19)
	2	4 (2)	1 (6)	3 (2)	2 (3)	1 (1)
Progression of disease within 24 months[c]	Yes	51 (32)	5 (28)	46 (33)	21 (30)	25 (36)
	Missing	9 (6)	4 (22)	5 (3)	1 (1)	4 (6)
Refractory to the last regimen		17 (11)	5 (28)	12 (8)	5 (7)	7 (10)
Number of prior antilymphoma regimens >1 line		19 (12)	5 (28)	14 (10)	7 (10)	7 (10)
	Missing	5 (3)	2 (11)	3 (2)	0 (0)	3 (4)
Prior rituximab—chemotherapy regimen		154 (97)	16 (89)	138 (98)	71 (100)	67 (96)
Prior anthracycline-based regimen		122 (77)	13 (72)	109 (77)	55 (77)	54 (77)
Prior bendamustine or fludarabine-based regimen		23 (15)	2 (11)	21 (15)	9 (13)	12 (17)
Prior rituximab—maintenance		86 (54)	8 (4)	78 (55)	44 (62)	34 (49)

Data are presented as n (%) unless indicated otherwise.
[a]At least determination.
[b]At enrollment.
[c]Relapse/progression <2 years of initial diagnosis

In the ITT randomized population, PFS (95% CI) was similar between the two groups (Figure 2A), with 33 (47%) events with ASCT (3-year PFS 62%, 49% to 73%; 6-year PFS 46%, 33% to 58%; median PFS 62 months) and 32 (45%) with radioimmunotherapy (3-year PFS 62%, 49% to 72%; 6-year PFS 52%, 38% to 63%; median PFS 78 months; HR 1.11, 95% CI 0.69-1.80, $P = 0.6662$).

An exploratory multivariable analysis indicated that refractory status at enrollment and POD24 were associated with worse PFS (enrollment HR 2.65, 95% CI 1.28-5.49, $P = 0.008$; POD24 HR 2.61, 95% CI 1.52-4.48, $P = 0.001$; Table 2). The results were the same in the entire population (Supplementary Material S1, Table S1, available at https://doi.org/10.1016/j.annonc.2023.10.095).

According to subgroup analysis, in the small population with refractory disease, ASCT seemed to perform better than radioimmunotherapy (HR 0.11 versus 1.27, interaction $P = 0.001$). Moreover, a trend in favor of radioimmunotherapy was noted in patients with stage I-II disease at enrollment (HR 5.64 versus 0.75 with ASCT, interaction $P = 0.09$). No other investigated variables (e.g. sex, age, FL histology, ECOG performance stage, lactate dehydrogenase, extranodal sites, and POD24) showed any PFS difference between the consolidation strategies (Supplementary Material S1, Figure S3, available at https://doi.org/10.1016/j.annonc.2023.10.095).

OS, EFS, and TFS. The 3- and 6-year OS (95% CI) rates of the enrolled population calculated from study inclusion were 87% (81% to 92%) and 77% (68% to 83%), respectively. The median OS for the enrolled population was not reached. The 3- and 6-year OS (95% CI) rates for the randomized population were 87% (79% to 91%) and 77% (68% to 84%). The OS (95% CI) rates were similar between the two consolidation groups. At 3 and 6 years, OS rates were 87% (76% to 93%) and 76% (63% to 86%) with ASCT versus 86% (74% to 92%) and 78% (65% to 87%) with radioimmunotherapy, respectively (HR 0.94, 95% CI 0.45-1.94, $P = 0.8588$; Figure 2B). The median OS for the randomized population was not reached in both arms.

The 3- and 6-year EFS (95% CI) rates for the enrolled population were 38% (30% to 45%) and 27% (20% to 35%),

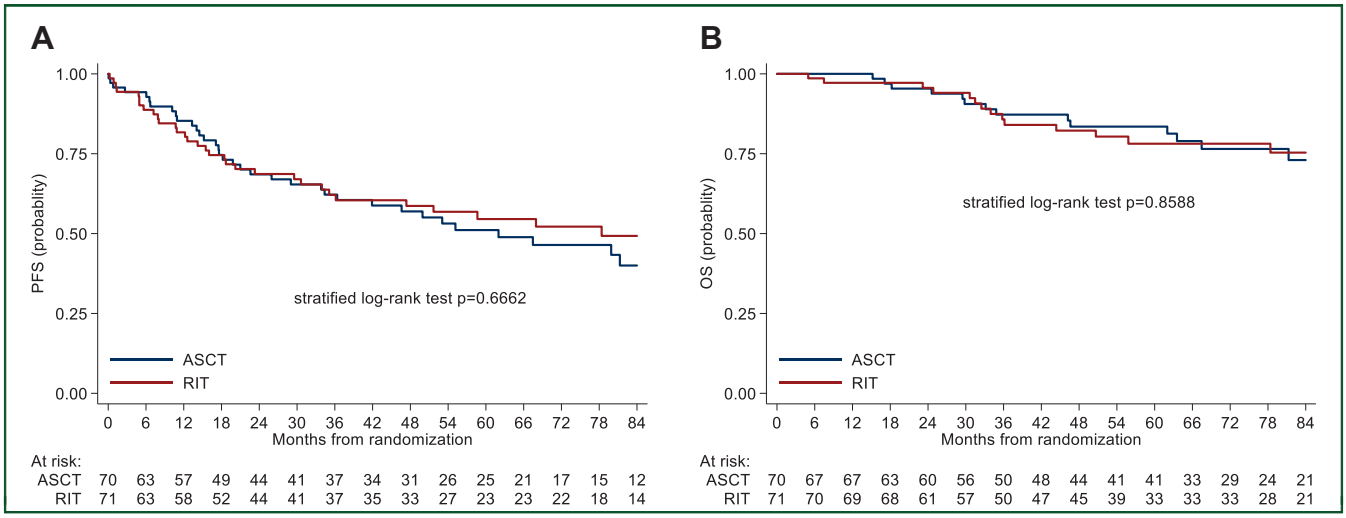

Figure 2. **(A)** PFS randomized population. **(B)** OS randomized population.
ASCT, autologous stem cell transplantation; OS, overall survival; PFS, progression-free survival; RIT, radioimmunotherapy.

respectively. The median EFS was 24 months (95% CI 19-30). The EFS rates were similar between the two consolidation groups. At 3 and 6 years, EFS (95% CI) rates were 38% (26% to 49%) and 27% (17% to 39%) with ASCT versus 42% (31% to 54%) and 33% (22% to 45%) with radioimmunotherapy, respectively (HR 1.19, 95% CI 0.79-1.80, $P = 0.3963$; see Supplementary Material S1, available at https://doi.org/10.1016/j.annonc.2023.10.095). The median EFS was 23 months in the ASCT group and 25 months in the radioimmunotherapy group. Likewise, TFS was similar between groups. At 3 and 6 years, TFS (95% CI) rates were 80% (65% to 89%) and 74% (58% to 85%) with ASCT compared with 78% (65% to 87%) and 78% (65% to 87%) with radioimmunotherapy, respectively (HR 1.09, 95% CI 0.50-2.39, $P = 0.8340$; Supplementary Material S1, Figure S4, available at https://doi.org/10.1016/j.annonc.2023.10.095).

Safety

During induction, no toxic death was reported. During maintenance, there was one death unrelated to lymphoma (1%) in the radioimmunotherapy arm (one acute myelogenous leukemia) and one death (1%) from pneumonia in the ASCT group. During follow-up, we recorded two deaths in the radioimmunotherapy arm from SARS-CoV-2 infection.

During induction, 60 (32%) of 159 patients had grade 3-4 hematological AEs, most frequently following R-DHAP. The most frequent hematological AE was neutropenia, which occurred in 38 (24%) patients overall during the induction phase (Supplementary Material S1, Table S2, available at https://doi.org/10.1016/j.annonc.2023.10.095). Further details on hematological AEs during the induction phase are given in Supplementary Material S1, available at https://doi.org/10.1016/j.annonc.2023.10.095.

During induction, 9% ($n = 14$) of all enrolled patients had grade 3-4 nonhematological AEs. The most frequent of these events was gastrointestinal, which occurred in 39 (25%) patients, more commonly after R-DHAP therapy [21 (35%), Supplementary Material S1, Table S3, available at https://doi.org/10.1016/j.annonc.2023.10.095].

After randomization, we reported 75 (54%) grade 3-4 hematological AEs and 6 (4%) grade 3-4 nonhematological

Table 2. Multivariable analysis on progression-free survival from randomization

Analysis variables	Hazard ratio	95% Confidence interval	*P*
Autologous stem cell transplantation versus radioimmunotherapy	0.99	0.59-1.65	0.965
Age at consent, per 1-point increase	1.02	0.99-1.05	0.210
Male gender	2.42	1.42-4.12	0.001
Ann Arbor stage III-IV	1.52	0.72-3.20	0.276
Eastern Cooperative Oncology Group performance status ≥1	1.00	0.52-1.93	0.996
High lactate dehydrogenase	2.36	1.32-4.23	0.004
At least one extranodal positive	1.86	1.04-3.32	0.037
Systemic symptoms B	1.23	0.62-2.44	0.547
Enrolled status[a]			
First progression (reference)	1	—	—
Second progression	1.04	0.40-2.74	0.929
Refractory	2.65	1.28-5.49	0.008
Progression of disease within 24 months[a]			
No (ref)	1	—	—
Yes	2.61	1.52-4.48	0.001
Miss/Unknown/Not applicable	0.87	0.19-3.92	0.854

[a]Enrolled status and progression of disease within 24 months are not adjusted to each other.

AEs during the blinded mobilization phase (Supplementary Material S1, available at https://doi.org/10.1016/j.annonc.2023.10.095). During consolidation, 29 (46%) patients in the radioimmunotherapy safety population had grade 3-4 hematological AEs, compared with 55 (93%) patients in the ASCT group (Fisher's exact test $P < 0.0001$; Table 3). Grade 3-4 nonhematological AEs occurred in three (5%) patients in the radioimmunotherapy safety population and 22 (37%) patients in the ASCT group ($P < 0.0001$), mostly caused by gastrointestinal disorders [20 (37%) of 60 patients in the ASCT group versus no events in the radioimmunotherapy group, $P < 0.0001$; Table 3]. During maintenance, 7 (13%) patients in the radioimmunotherapy safety population reported grade 3-4 hematological events, compared with 13 (25%) in the ASCT population ($P = 0.168$). Further details are provided in Supplementary Material S1, available at https://doi.org/10.1016/j.annonc.2023.10.095.

Among the 159 patients, we recorded noncutaneous solid tumors in five (3%, one in the radioimmunotherapy group and four in the ASCT arm), skin cancers in two (1%, all in the ASCT arm), and secondary myelodysplastic syndrome or acute myeloid leukemia in five (3%, two in the radioimmunotherapy group and three in the ASCT arm, one received R-CHOP as induction and four R-B). One (6%) of 18 patients in the nonrandomized population had a secondary malignancy (cumulative incidence 7.1%, 95% CI 0.5% to 27.5%, 36 months after enrollment) compared with 10 (7%) of 141 patients in the randomized population (cumulative incidence 6.4%, 95% CI 4.5% to 15.1%, 36 months after enrollment). One of these 10 secondary tumors was fatal. Secondary malignancies were reported in three (4%) patients in the radioimmunotherapy safety population and seven (10%) patients in the ASCT group. The cumulative incidence (95% CI) of any secondary malignancy at 36 months was 7.4% (2.4% to 16.5%) in the ASCT group versus 5.7% (1.5% to 14.2%) in the radioimmunotherapy safety population (HR 1.65, 95% CI 0.41-6.70, $P = 0.480$).

DISCUSSION

The FIL FLAZ-12 randomized phase III trial compared two widely used consolidation strategies (ASCT and radioimmunotherapy) in R/R FL. Both regimens were used in the context of a rituximab-dense program, with an anti-CD20 antibody used during both induction (five doses) and maintenance (eight doses). The main results of our study do not support any efficacy superiority of ASCT versus radioimmunotherapy and confirm a higher toxicity and clinical complexity with ASCT. Most notably, PFS differences were not observed at both 3 years (the primary endpoint of the study) and in the long term-analysis at 6 years. No differences were observed also in terms of OS, EFS, and TFS.

For decades, ASCT has been considered a good consolidation strategy following rituximab chemotherapy in R/R FL. Evidence for this indication stemmed from the CUP trial,[16] which compared ASCT with no further treatment in the pre-rituximab era and showed an impressive benefit with ASCT. Our study had a different design from that trial, as ASCT was compared with radioimmunotherapy rather than with further chemotherapy. Moreover, the CUP trial[16] was conducted in the pre-PET scan era and did not require tumor rebiopsy. Therefore the trial population probably included a substantial number of patients with transformed disease compared with our trial. Moreover, ASCT might exert a less prominent effect if rituximab is added in induction and maintenance, as in our study. In addition, one might speculate that rituximab maintenance might have equalized the benefit of the two consolidation programs. Regardless of which among several possible explanations may be correct, our study indicates that in a modern setting (which includes rituximab in both induction and maintenance) results achieved with ASCT are not superior to those achievable with radioimmunotherapy, which offers a considerably less toxic and demanding approach that is suitable for the outpatient setting.

The use of radioimmunotherapy as consolidation has been tested in the frontline setting, showing a substantial benefit versus no further treatment in a rituximab-free context. Morschhauser et al.[20] reported a better outcome with radioimmunotherapy, with a median PFS of 36.5 versus 13.3 months with no further treatment ($P < 0.0001$). FL cells are exquisitely sensitive to radiation-mediated killing, and radioimmunotherapy has an excellent safety profile. In terms of efficacy in the current trial, radioimmunotherapy performed as well as a highly toxic ASCT program. This finding suggests that radioimmunotherapy should be favorably considered even if logistical and practical considerations and limited availability hamper its wider use.

The main limitation of ibritumomab is that it uses CD20 as a target, which is already heavily exploited by naked antibodies and bispecifics. Radioimmunotherapy-based approaches focusing on alternative targets probably deserve further investigation. For example, CD37 is a highly promising target. A first-generation, single-dose CD37-directed radioimmunotherapy, 177Lu-lilotomab satetraxetan, has been extensively investigated in preclinical models and has shown efficacy in clinical trials, including a phase I/IIa study.[29]

Our study first evaluated ASCT or radioimmunotherapy consolidation strategies in the context of immunological maintenance. The therapeutic role of rituximab maintenance is better described following first-line treatment or salvage treatment. The European pivotal phase III study conducted by van Oers et al.[17] (EORTC 20981) demonstrated the advantage of rituximab maintenance given every 3 months for a maximum of 2 years compared with observation alone. Its benefit after ASCT or radioimmunotherapy also has been investigated exclusively in a small nonrandomized series, showing durable responses and an improved CRR in patients with untreated indolent lymphomas.[21] Our trial findings confirm that rituximab maintenance is similarly feasible after radioimmunotherapy and ASCT, possibly contributing to the clinical activity of both schedules.

Our study has several limitations, including a prolonged enrollment period and premature discontinuation. Despite

Table 3. Randomized population adverse events during mobilization, consolidations, and maintenance phases

	Mobilization (N = 138)		Radioimmunotherapy (n = 63)		Autologous stem cell transplantation (n = 59)		Maintenance radioimmunotherapy (n = 56)		Maintenance autologous stem cell transplantation (n = 53)	
CTCAE grade	1-2	≥3	1-2	≥3	1-2	≥3	1-2	≥3	1-2	≥3
Hematological	5 (4)	95 (69)	5 (8)	29 (46)	—	55 (93)	13 (23)	7 (13)	8 (15)	13 (25)
Granulocytes	8 (6)	75 (54)	2 (3)	26 (41)	1 (2)	53 (90)	8 (14)	5 (9)	7 (13)	12 (23)
Hemoglobin	70 (51)	15 (11)	22 (35)	2 (3)	38 (64)	15 (25)	10 (18)	—	8 (15)	—
Platelets	2 (2)	92 (67)	9 (14)	23 (37)	1 (2)	54 (92)	10 (18)	2 (4)	8 (15)	1 (2)
White blood cells	14 (10)	75 (54)	10 (16)	17 (27)	1 (2)	52 (88)	10 (18)	5 (9)	11 (21)	5 (9)
Febrile neutropenia	—	6 (4)	—	—	0 (0)	19 (32)	—	—	—	—
Nonhematological	22 (16)	6 (5)	11 (17)	3 (5)	17 (29)	22 (37)	22 (39)	—	17 (32)	3 (6)
Cardiac disorders	1 (1)	—	1 (2)	—	1 (2)	—	2 (4)	—	1 (2)	—
Ischemia/Infarct	1 (1)	—	—	—	—	—	—	—	—	—
Palpitations	—	—	—	—	—	—	—	—	1 (2)	—
Supraventricular arrhythmia	—	—	1 (2)	—	—	—	—	—	—	—
Tinnitus	—	—	—	—	—	—	2 (4)	—	1 (2)	—
Restrictive cardiomyopathy	—	—	—	—	1 (2)	—	—	—	—	—
Eye disorders	1 (1)	—	—	—	—	—	—	—	—	—
Eye pain	1 (1)	—	—	—	—	—	—	—	—	—
Gastrointestinal disorders	12 (9)	1 (1)	2 (3)	—	12 (20)	20 (34)	6 (11)	—	8 (15)	1 (2)
Constipation	4 (3)	—	—	—	1 (2)	—	2 (4)	—	2 (4)	—
Diarrhea	—	1 (1)	—	—	12 (20)	6 (10)	6 (11)	—	7 (14)	1 (2)
Flatulence	—	—	—	—	—	—	—	—	—	—
Gastritis	—	—	—	—	—	—	1 (2)	—	1 (2)	—
Mucositis	2 (2)	—	—	—	9 (15)	18 (31)	—	—	—	—
Nausea	6 (5)	—	2 (3)	—	—	1 (2)	—	—	1 (2)	—
Pancreatitis	—	—	—	—	—	—	—	—	1 (2)	—
Gastrointestinal pain	—	—	—	—	—	—	—	—	1 (2)	—
Vomiting	3 (2)	—	—	—	—	1 (2)	—	—	—	—
General disease and administration site conditions	9 (7)	—	8 (13)	1 (2)	6 (10)	1 (2)	11 (20)	—	8 (15)	—
Fatigue	4 (3)	—	8 (13)	—	1 (2)	—	6 (11)	—	3 (6)	—
Fever	4 (3)	—	—	1 (2)	5 (9)	1 (2)	5 (9)	—	5 (10)	—
Injection site reaction	—	—	—	—	1 (2)	—	—	—	—	—
Flu-like symptoms	1 (1)	—	—	—	—	—	—	—	1 (2)	—
Hepatic failure	1 (1)	—	—	—	—	—	—	—	1 (2)	—
Pain	—	—	—	1 (2)	—	—	—	—	—	—
Hypothermia	—	—	—	—	—	—	1 (2)	—	—	—
Infections and infestations	5 (4)	5 (4)	—	2 (3)	9 (15)	4 (7)	10 (18)	—	9 (17)	1 (2)
Lung	1 (1)	—	—	—	—	1 (2)	5 (9)	—	2 (4)	1 (2)
Sepsis	—	5 (4)	—	1 (2)	3 (5)	2 (3)	—	—	—	—
Mucosal	—	—	—	—	1 (2)	1 (2)	1 (2)	—	2 (4)	—
Catheter related	1 (1)	—	—	—	—	—	—	—	—	—
Conjunctiva	1 (1)	—	—	—	—	—	—	—	—	—
Bacterial NOS	2 (2)	—	—	1 (2)	—	—	6 (11)	—	4 (8)	1 (2)
Viral	—	—	—	—	1 (2)	—	1 (2)	—	4 (8)	—
Fungal NOS	1 (1)	—	—	—	—	—	—	—	—	—
Investigation	2 (2)	—	1 (2)	1 (2)	1 (2)	—	1 (2)	—	1 (2)	—
ALT increased	—	—	1 (2)	—	1 (2)	—	1 (2)	—	1 (2)	—
AST increased	—	—	—	—	—	—	—	—	—	—
Blood bilirubin increased	1 (1)	—	—	1 (2)	—	—	—	—	1 (2)	—
Creatinine increased	1 (1)	—	—	—	—	—	—	—	—	—

Continued

Table 3. Continued

	Mobilization ($N = 138$)		Radioimmunotherapy ($n = 63$)		Autologous stem cell transplantation ($n = 59$)		Maintenance radioimmunotherapy ($n = 56$)		Maintenance autologous stem cell transplantation ($n = 53$)	
Metabolism and nutrition disorders	1 (1)	—	—	—	—	—	1 (2)	—	2 (4)	—
Hyperglycemia	—	—	—	—	—	—	1 (2)	—	1 (2)	—
Hyperuricemia	—	—	—	—	—	—	—	—	1 (2)	—
Hypokalemia	1 (1)	—	—	—	—	—	—	—	—	—
Musculoskeletal and connect tissue disorders.	2 (2)	—	3 (5)	—	—	—	6 (11)	—	1 (2)	—
Back pain	—	—	—	—	—	—	1 (2)	—	—	—
Bone pain	1 (1)	—	1 (2)	—	—	—	5 (9)	—	—	—
Muscle weakness upper limb	—	—	1 (2)	—	—	—	—	—	—	—
Generalized muscle weakness	—	—	1 (2)	—	—	—	—	—	—	—
Myalgia	—	—	—	—	—	—	2 (4)	—	1 (2)	—
Nervous system disorders	1 (1)	—	1 (2)	—	—	1 (2)	3 (6)	—	2 (4)	—
Headache	—	—	—	—	—	—	—	—	—	—
Acoustic nerve disorder NOS	—	—	—	—	—	—	1 (2)	—	2 (4)	—
Peripheral motor neuropathy	1 (1)	—	1 (2)	—	—	—	1 (2)	—	1 (2)	—
Paresthesia	—	—	—	—	—	—	1 (2)	—	—	—
Peripheral sensory neuropathy	—	—	—	—	—	—	1 (2)	—	—	—
Tremor	—	—	—	—	—	—	—	—	—	—
Cranial neuropathy	—	—	—	—	—	1 (2)	—	—	—	—
Depression	—	—	—	—	—	—	1 (2)	—	—	—
Renal and urinary disorders	—	—	—	—	—	1 (2)	2 (4)	—	1 (2)	—
Acute kidney injury	—	—	—	—	—	1 (2)	1 (2)	—	—	—
Urinary retention	—	—	—	—	—	—	1 (2)	—	—	—
Renal colic	—	—	—	—	—	—	2 (4)	—	—	—
Respiratory, thoracic, and mediastinal disorders	2 (2)	—	1 (2)	—	—	—	4 (7)	—	4 (8)	—
Cough	1 (1)	—	1 (2)	—	—	—	4 (7)	—	4 (8)	—
Dyspnea	—	—	—	—	—	—	—	—	—	—
Pharyngolaryngeal pain	1 (1)	—	—	—	—	—	—	—	—	—
Skin and subcutaneous tissue disorders	2 (2)	—	1 (2)	—	4 (7)	—	—	—	—	—
Skin other	—	—	1 (2)	—	3 (5)	—	—	—	2 (4)	—
Pruritus	—	—	—	—	—	—	—	—	2 (4)	—
Rash	2 (2)	—	—	—	1 (2)	—	—	—	—	—
Urticaria	—	—	—	—	—	—	—	—	—	—
Vascular disorders	1 (1)	—	1 (2)	—	2 (3)	—	—	—	1 (2)	—
Phlebitis	—	—	—	—	—	—	—	—	—	—
Other hemorrhage	—	—	1 (2)	—	1 (2)	—	—	—	—	—
Hypertension	—	—	—	—	—	—	—	—	1 (2)	—
Hypotension	—	—	—	—	1 (2)	—	—	—	—	—
Thromboembolic event	1 (1)	—	—	—	—	—	—	—	—	—

Data are presented as *n* (%) unless stated otherwise.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; NOS, not otherwise specified.

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these limitations, the enrolled population appears to be representative of an R/R FL cohort, and the prolonged median follow-up (77 months for the randomized population) partially mitigated the loss of statistical power. The implications of our study findings, with a 95% lower limit of 0.69 for PFS HR, are that a hypothesized benefit of ASCT in improving PFS (HR 0.56) is highly unlikely.

Clearly, the treatment of FL is rapidly changing, with a straightforward shift toward noncytotoxic/non-DNA-damaging treatments instead of chemotherapy. Good results observed with the combination of an anti-CD20 (rituximab or obinutuzumab) and lenalidomide[30-32] and with the obinutuzumab/zanubrutinib[31] combination are clearly indicative of a paradigm shift. This shift will be further enhanced by novel treatments such as novel antibodies and novel cell therapies entering routine treatment.[30-38] There is little doubt that in the context of novel treatments, chemotherapy-based consolidation will find limited room for use. Our study indicates that ASCT should no longer be considered intrinsically superior to less intensified programs and therefore its use appears no longer justified, particularly considering its toxicity. By contrast, the observation that radio immunotherapy consolidation provided good disease control with little toxicity may suggest that consolidation approaches with agents at lower toxicity could be a reasonable strategy. Conversely, despite a full program with salvage chemoimmunotherapy, consolidation, and maintenance as used in our study, the overall results showed a continuous tendency to relapse (3- and 6-year PFS rate of 60% and 44%). This highlights a different strategy including a long-term treatment with novel immunotherapy as bispecific antibodies and/or biological agents at low toxicity. Both strategies are worthy of future investigations to improve the outcome of patients with R/R FL.

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REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375-2390.
2. Tellier J, Menard C, Roulland S, et al. Human t(14;18)positive germinal center B cells: a new step in follicular lymphoma pathogenesis? *Blood*. 2014;123(22):3462-3465.
3. Batlevi CL, Sha F, Alperovich A, et al. Follicular lymphoma in the modern era: survival, treatment outcomes, and identification of high-risk subgroups. *Blood Cancer J*. 2020;10:74.
4. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*. 2004;104:3064-3071.
5. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*. 2005;106:3725-3732.
6. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol*. 2008;26:4579-4586.
7. Weide R, Hess G, Köppler H, et al. High anti-lymphoma activity of bendamustine/mitoxantrone/rituximab in rituximab pretreated relapsed or refractory indolent lymphomas and mantle cell lymphomas. A multicenter phase II study of the German Low Grade Lymphoma Study Group (GLSG). *Leuk Lymphoma*. 2007;48:1299-1306.
8. 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;377:42-51.

9. Salles GA, Seymour JF, Feugier P, et al. Long term follow-up of the PRIMA study: half of patients receiving rituximab maintenance remain progression free at 10 years. *Blood*. 2017;130:486.
10. 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*. 2019;37:2815-2824.
11. 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*. 2018;36:689-696.
12. Morschhauser F, Fowler NH, Feugier P, et al. Rituximab plus lenalidomide in advanced untreated follicular lymphoma. *N Engl J Med*. 2018;379:934-947.
13. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381:1203-1210.
14. Gribben JG. How I treat indolent lymphoma. *Blood*. 2007;109:4617-4626.
15. Dreyling M, Ghielmini M, Rule S, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32:298-308.
16. Schouten HC, Qian W, Kvaloy S, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. *J Clin Oncol*. 2003;21:3918-3927.
17. van Oers MH, Klasa R, Marcus RE, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial. *Blood*. 2006;108(10):3295-3301.
18. Casulo C, Friedberg JW, Ahn KW, et al. Autologous transplantation in follicular lymphoma with early therapy failure: a National LymphoCare Study and Center for International Blood and Marrow Transplant Research Analysis. *Biol Blood Marrow Transplant*. 2018;24(6):1163-1171.
19. Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2002;20:2453-2463.
20. 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*. 2008;26:5156-5164.
21. Karmali R, Kassar M, Venugopal P, et al. Safety and efficacy of combination therapy with fludarabine, mitoxantrone, and rituximab followed by yttrium-90 ibritumomab tiuxetan and maintenance rituximab as front-line therapy for patients with follicular or marginal zone lymphoma. *Clin Lymphoma Myeloma Leuk*. 2011;11:467-474.
22. Campo E, Swerdlow SH, Harris NL, et al. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood*. 2011;117(19):5019-5032.
23. Barosi G, Carella A, Lazzarino M, et al. Management of nodal indolent (non marginal-zone) non-Hodgkin's lymphomas: practice guidelines from the Italian Society of Hematology, Italian Society of Experimental Hematology and Italian Group for Bone Marrow Transplantation. *Haematologica*. 2005;90:1236-1257.
24. Brice P, Bastion Y, Lepage E, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 1997;15(3):1110-1117.
25. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25(5):579-586.
26. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-3212.
27. Klastersky J, Naurois J, Rolston K, et al. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2016;27(suppl 5):v111-v118.
28. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med*. 1999;18(6):695-706.
29. Kolstad A, Illidge T, Bolstad N, et al. Phase 1/2a study of 177Lu-lilotomab satetraxetan in relapsed/refractory indolent non-Hodgkin lymphoma. *Blood Adv*. 2020;4(17):4091-4101.
30. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. *J Clin Oncol*. 2019;37(14):1188-1199.
31. Morschhauser F, Le Gouill S, Feugier P, et al. Obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma (GALEN): a multicentre, single-arm, phase 2 study. *Lancet Haematol*. 2019;6(8):e429-e437.
32. Strati P, Jain P, Johnson RJ, et al. Long-term follow-up of lenalidomide and rituximab as initial treatment of follicular lymphoma. *Blood*. 2021;137(8):1124-1129.
33. Zinzani PL, Mayer J, Auer R, et al. Zanubrutinib plus obinutuzumab (ZO) versus obinutuzumab (O) monotherapy in patients (pts) with relapsed or refractory (R/R) follicular lymphoma (FL): primary analysis of the phase 2 randomized ROSEWOOD trial. *J Clin Oncol*. 2022;40(suppl 16):7510.
34. Sapon-Cousineau V, Sapon-Cousineau S, Assouline S. PI3K inhibitors and their role as novel agents for targeted therapy in lymphoma. *Curr Treat Options Oncol*. 2020;21:51.
35. Budde LE, Sehn LH, Matasar MJ, et al. Mosunetuzumab monotherapy is an effective and well-tolerated treatment option for patients with relapsed/refractory (R/R) follicular lymphoma (FL) who have received $\geq$2 prior lines of therapy: pivotal results from a phase I/II study. *Blood*. 2021;138:127.
36. Hutchings M, Morschhauser F, Iacoboni G, et al. Glofitamab, a novel, bivalent CD20-targeting T-cell-engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-cell lymphoma: a phase I trial. *J Clin Oncol*. 2021;39:1959-1970.
37. Hutchings M, Mous R, Clausen MR, et al. Subcutaneous epcoritamab induces complete responses with an encouraging safety profile across relapsed/refractory B-cell non-Hodgkin lymphoma subtypes, including patients with prior CAR-T therapy: updated dose escalation data. *Blood*. 2020;136(suppl 1):45-46.
38. Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. *Lancet Oncol*. 2022;23(1):91-103.