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Review article

Follicular Lymphoma: The Management of Elderly Patient

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Abstract. Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma, which typically affects mature adults and elderly, whose median age at diagnosis is 65 years. The natural history of FL appears to have been favorably impacted by the introduction of Rituximab. Randomized clinical trials demonstrated that the addition of rituximab to standard chemotherapy induction has improved the overall survival and new strategies of chemo-immunotherapy, such as Bendamustine combined with Rituximab, showed optimal results on response and reduced hematological toxicity, becoming one of the standard treatments, particularly in elderly patients. Moreover, maintenance therapy with Rituximab demonstrated improvement of progression-free survival. Despite these exciting results, FL is still an incurable disease. It remains a critical unmet clinical need finding new prognostic factors to identify poor outcome patients better, to reduce the risk of transformation and to explore new treatment strategies, especially for patients not candidate to intensive chemotherapy regimens, such as elderly patients. Some progress was already reached with novel agents, but larger and more validated studies are needed. Elderly patients are the largest portion of patients with FL and represent a subgroup with higher treatment difficulties, because of comorbidities and smaller spectrum for treatment choice. Further studies, focused on elderly follicular lymphoma patients, with their peculiar characteristics, are needed to define the best-tailored treatment at diagnosis and at the time of relapse in this setting.

Keywords: Follicular Lymphoma, Elderly, Comorbidities.

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Introduction. Follicular lymphoma (FL) is the most common form of indolent lymphoma and accounts for 20% to 30% of all newly diagnosed non-Hodgkin's Lymphoma (NHL)[1] and with an annual incidence of 1.6- 3.1/ 100000 cases in western countries.[2,3] It typically occurs in mature and older adults, the median age of 65 years and with frequently in patients older than 75 years. FL is considered as an indolent but incurable disease with a median life expectancy of approximately ten years. Despite advances in the treatment of FL, most of the patients remain incurable and, in 10 years, 15% to 28% of cases will transform into an aggressive phenotype, typically diffuse large B-cell lymphoma (DLBCL).

FL arises from malignant transformation of normal germinal center (GC) B cells and, in approximately 85% of cases, harbours the translocation (14;18)(q32;q21), resulting in an inability to down-regulate expression of the anti-

apoptotic protein B-cell lymphoma 2 (BCL2), which is absent in normal GC B cells.[4] Most tumors are characterized by recurrent secondary genetic alterations that may provide a growth advantage, including genomic gains, losses, and mutations.

The histological report should give the diagnosis according to the World Health Organization (WHO) classification.[5] Grading of lymph node biopsies is performed according to a number of blasts/high power field.

The treatment depends on the stage of the disease, so initial staging should be thorough, particularly in the small proportion of patients with localized stages I and II (10%–15%). Staging should include a computed tomography (CT) scan, Positron emission tomography(PET)-CT and a bone marrow aspirate and biopsy.[6] Complete blood test, including chemistry and screening for HIV, HCV, and HBV must be done at baseline. The staging is performed according to the Ann Arbor classification system.[7]

The prognosis of FL remains heterogeneous. Thus, prognostic indices are necessary to guide the physician's decision-making process and to design clinical trials. Several prognostic factors have been identified in patients with FL, including age, stage, tumor burden, bone marrow (BM) involvement, systemic symptoms, performance status (PS), serum lactate dehydrogenase (LDH),

hemoglobin, erythrocyte sedimentation rate, and β2-microglobulin.[8-9]

As result of international cooperation, the FL International Prognostic Index (FLIPI) was established in 2004.[10] This model divided patients affected by FL in three different classes of risk according to five parameters, including age over 60 years, Ann Arbor stage III or IV, hemoglobin value < 12 mg/dL, more than four nodal sites involved, increased value of serum LDH. However, the FLIPI was born before rituximab era and was based on retrospective data, so a revised FLIPI 2 (incorporating beta2 microglobulin, the diameter of largest lymph node, bone marrow involvement, and hemoglobin level) was introduced.[11]

Extended knowledge of the biology of tumor lead to a clinic-genetic risk score (m7-FLIPI) based on mutation status of 7 candidate genes,[12] but it is not standardized yet.

Elderly Patient: the Impact of Age. Many patients with FL are elderly and age by itself (>60 years) has been shown to be one of the most powerful poor prognostic features into Follicular Lymphoma International Prognostic Index (FLIPI).[10] However, so far there are few clinical trials specifically designed for these patients; in clinical practice elderly patients are often managed in a palliative way or with the adoption of a "watchful waiting" policy in low tumor burden or asymptomatic patients or, in most of the cases, the planned whole treatment is stopped because of treatment-related toxicity.

The clinical approach to elderly patients is a complex issue and age alone could not be enough to guide the treatment strategy. Older patients show alterations in tumor-host biology and comorbidities which result in changes in pharmacokinetics and pharmacodynamics, may be a possible reason for poorer outcome in this setting.[13-14] Moreover, it is well known that immune system in older adults displays a deterioration of DNA-damage repair mechanisms and a decrease of both cellular mediated and humoral immune response.[15-16]

Older patients are also more likely to develop cardiotoxicity, neurotoxicity, kidney injury, and mucositis.

Indeed, to explain the worst prognosis in elderly patients, some studies suggested that lymphomas could be biologically more complex and aggressive in older people.

Some evidence suggested for example that CD69 expression on lymphoma cells was related to a poor outcome, with a prognostic value independent from the treatment, evaluated in a population of older adults.[12] A dense infiltrate of CD4-positive T cells, especially when located interfollicular, was a good prognostic sign irrespective of treatment. Dense infiltrate of FoxP3-positive T cells and CD68 positive macrophage, especially with an interfollicular component, was associated with better survival. However, contradictory results regarding the correlation between treatment heterogeneity and clinical impact have been reported by a Finnish group:[17] they showed that the addition of rituximab to chemotherapy is the cause of reversing the negative prognostic impact of high macrophage content, showed in previous series,[18] into favorable factor. In the rituximab era, the high macrophage content showed a positive impact on

prognosis at both diagnosis and relapse, and it is likely to be associated with antibody-dependent cytotoxicity. It was noted that the relative number of lymphoma-associated macrophage is lower in younger patients..[18-19] Also, the prognostic value of minimal residual disease (MRD) was firstly evaluated in a cohort of elderly patients.[20]

Even if in elderly patients there were biological differences compared to FL in younger people, many trials showed that these patients, if treated with a correct dose-intensity chemotherapy, could reach a response rate similar to a younger population.[15]

According to the results of these studies, an accurate, complete evaluation of elderly patients affected by lymphoma remains a central issue for a good clinical practice, in order to administer a tailored dose-intensity therapy to obtain the best outcome for these patients.

The Comprehensive Geriatric Assessment (CGA) is a score used to make a whole evaluation of elderly people with cancer, based on age, comorbidities and functional abilities of daily living and it represents an important tool in older people, in order to personalize the treatment discriminating among fit, unfit or frail patients.[21] It is based on many different tests including: ADL scale, IADL scale, evaluation of comorbidities (Charlson's scale and CIRS-G scale), Mini Mental State Examination (MMSE), evaluation of nutritional state (20% of patients older than 70 years is underfed)[22] and socio-economic state. ADL scale (or Katz's scale)[23] is based on the possibility to perform regular daily activities (such as eating, washing, dressing, etc..); IADL scale (or Lawton's scale)[24] evaluates the self-government in social function, such as phoning, shopping, money management, etc. MMSE shows alterations in more than 50% of people older than 85 years[25] and Geriatric Depression Scale demonstrates a depression in 20% of patients older than 70 years.[26]

On this basis, Tucci et al.[27] conducted a pilot trial to analyze if a simplified CGA model could identify elderly patients with aggressive lymphoma eligible for anthracycline therapy on 84 patients aged more than 65 years. The Italian Lymphoma Foundation (FIL) recently performed a prospective multicenter trial to validate a simplified CGA evaluation model in a cohort of 173 elderly patients with lymphoma. Based on this simplified CGA elderly patients were classified into three categories: fit, unfit and frail **(Figure 1)**. The results of this study showed that the 2y-OS was significantly better in fit than in unfit or frail patients (84% vs. 47%, p <0.0001). Survival in unfit and frail people was superimposable. CGA was confirmed as very useful to guide clinical therapeutic decisions and to identify elderly patients who can benefit from a curative approach, while further efforts are needed to better tailor therapies in not fit population.[28] However, it must be noted that this trial was conducted in patients with aggressive diffuse large B-cell lymphoma and it was not validated in a cohort of FL elderly patients.

SCALE	FIT	UNFIT	FRAIL
ADL	6	5*	≤4*
IADL	8	7- 6*	≤5*
CIRS	0 score = 3-4 < 5 score = 2	0 score = 3-4 5-8 score = 2	1 score = 3-4 > 8 score = 2
AGE		≥ 80 fit	≥ 80 unfit

Figure 1. Simplified Comprehensive Geriatric Assessment score.[27]

Recommendations of the Authors: an accurate whole evaluation of elderly patient affected by lymphoma is a central issue, and it represents the first step for a tailored dose-intensity therapy, to obtain the best outcome for these patients; CGA and comorbidity scale are useful instruments to guide therapeutic decisions for a good clinical practice.

Treatment. An ideal therapy for older adults should be brief, feasible in an outpatient setting, effective and possibly with low related toxicity.

Despite a variety of treatment approaches are currently available for the initial treatment of follicular lymphoma, there are no universally accepted first-line chemotherapy regimens for advanced stage disease. The introduction of anti-CD20 monoclonal antibody (Rituximab) has definitely improved the outcome of these patients as shown by many studies. Rituximab and standard chemotherapy show no significant overlapping toxicities. This evidence provides the rationale for combining chemotherapy regimens with Rituximab, considered at present the standard component of first-line treatment with a complete remission rate ranging from 20 to 75%, a 4 years-progression free survival (4y-PFS) improved at 61% (p=0.005) and a 4y-overall survival (4y-OS) of 91% (p < 0.001).[29]

First-Line Therapy. In the small proportion of limited non-bulky stages I–II, radiotherapy alone is the preferred choice. Several centers reviewed the long-term outcome of RT alone and demonstrated a freedom from relapse of 55%, 44%, 43% and 35% at 5, 10, 15 and 20 years of follow-up. Relapse occurs in only 10% of high-risk patients at 10 years.[30-31]

The most recent and largest retrospective study of 6,568 patients with follicular lymphoma stage I or II diagnosed between 1973 and 2004 was based on SEER data. Compared to the no RT group, patients who received RT had higher rates of disease-specific survival (DSS) at 5 (81 % vs. 90%), 10 (66 % vs. 79%), 15 (57 % vs. 68%), and 20 (51 % vs. 63%) years. Overall survival was also improved for patients who received initial RT. Relapses usually occur distant from the RT site and are rare after 10 years (1-11 %).[32] Data demonstrates that RT involved filed 24 Gy is indicated to obtain a curative intent, whereas low dose schedule (2x2 Gy) shows mainly a palliative effect.[33]

An initial strategy of observation can also be considered. A Stanford report of stage I and II patients who received no initial therapy showed that more than half of the 43 patients did not require any therapy at a median of 6 years, and 85% of patients were alive at 10 years.[34] However this was performed in a small series of patients, and W&W must be considered in selected case to avoid the usual side effects of radiation (e.g. sicca syndrome, thyroid malfunction, mucositis, myeloablative suppression, bladder disorders).

Asymptomatic, low-tumor-burden patients may be candidates for a strategy of watch and wait. The Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria are commonly used to assess tumor burden. For high-tumor-burden FL, GELF criteria include at least 1 of the following: 3 distinct nodal sites, each ≥3 cm; single nodal site ≥7 cm; symptomatic splenomegaly; organ compression or compromise; pleural effusions, ascites. Therapy is indicated in the presence of 1 criteria of high-tumor-burden; B symptoms or any systemic symptoms; LDH or B2M above the upper limit of normal. In the absence of high-tumor-burden criteria, there are no benefits on overall survival by starting immediately specific treatment.[35] **(Table 1)**

The F2-study, which compared the first-line treatment with Rituximab to the Watch and Wait approach (W&W), did not show any differences on freedom from treatment failure (FFTF) andoverall survival rates after treatment in a selected prognostically favorable group. The median studied population age was similar in two groups, 59 years (range 33-94 yrs) in W&W arm and 56 years (range 23-83 yrs) in Rituximab receiving arm. Patients older than 60 years were respectively 46% and 39%.[36] Certainly, for elderly patients with a reduced life expectancy, a W&W strategy is most appropriate in a low-tumor-burden setting, as therapy is unlikely to alter the life expectancy and could have detrimental effects on quality of life.

V Table 1. High tumour burden criteria in Follicular Lymphomas [Groupe d'Etude des Lymphomes Folliculaires (GELF) and British National Lymphoma Investigation (BNLI)]. LDH: lactate dehydrogenase.[35]

Parameter	High tumour burden criteria
Lymph nodes	Bulk (>6 cm) or 3 lymph nodes in distinct areas >3 cm
Spleen	Symptomatic splenic enlargement
(Potential) complication	Organ compression by tumour, pleural or peritoneal effusion
Serum markers	Elevated LDH or elevated β_2-microglobuline
Clinical presentation	B symptoms

A systemic more aggressive therapy is indicated for advanced stage FL with high-tumor-burden or adverse prognostic features. At present, advanced stage FL is still considered incurable, even if the discovery and introduction of Rituximab as standard therapy in FL has dramatically improved overall survival (OR) and progression-free survival (PFS).[37-38] The optimal chemotherapy to associate with Rituximab remains unsettled, and in clinical decisions, age, comorbidities, and patients willingness have to be considered. The most common associations were R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone), and R-fludarabine, even if some of these options are not advisable in elderly patients for their severe hematological toxicity. A randomized comparison of these regimens indicated R-CHOP has the best risk-benefit profile, as it is more active than R-CVP and less toxic than Rituximab-fludarabine-mitoxantrone.[39]

In the last 20 years, the re-discovery of Bendamustine has opened a new scenario in Indolent Lymphoma treatment regimens. A phase 3 trial from the Study group Indolent Lymphoma

(StiL)[40] randomized 549 patients with high-tumor-burden indolent NHL and mantle cell lymphoma (median age 64 years) to receive bendamustine 90 mg/m2 on days 1 and 2, with rituximab 375 mg/m2 on day 1, every 28 days (the BR group) or to receive standard R-CHOP chemotherapy every 21 days. The overall response rates (ORRs) were similar in the two groups (92.7% vs. 91.3%, respectively), but the complete response (CR) was significantly higher in the BR group (39.8%) compared with the R-CHOP group (30.0%). Evaluating just the FL patients, with a median follow-up of 45 months, the median PFS was significantly longer after BR compared with R-CHOP (not reached vs. 40.9 months). OS did not differ. There was less hematologic toxicity, alopecia, infections, peripheral neuropathy, and stomatitis with BR.[40]

The successful results of Bendamustine in FL were also confirmed in a randomized, phase 3 trial (Bright) which enrolled 447 patients with untreated indolent NHL and mantle cell lymphoma (MCL) to received Rituximab-Bendamustine (BR) or standard therapy R-CHOP/R-CVP. 70% of study's population were FL with a median age of 60 years in BR group and 58 years in R-CHOP/R-CVP group. The authors demonstrated the no inferiority of BR to standard treatments, with ORR of 97% (CR in 31%) vs. 91% (CR 25%) respectively. The toxicity pattern was different, showing a higher incidence of nausea, vomiting and skin reactions in BR arm, but rarely severe events (3%). Even if GCSF was used mainly in R-CHOP, this group reported the higher number of cases of 3-4 grade neutropenia.[41]

Another possible choice of treatment in FL is Radioimmunotherapy, using an anti-CD20 antibody conjugated with a radionuclide, 90Y-ibritumomab tiuxetan (Zevalin). It is recommended in consolidation therapy, but it has also been evaluated in the first-line treatment of advanced stage FL. In a phase II trial Zevalin was administrated 8 days after a single dose of Rituximab (at 250 mg/mg). 50 patients were enrolled, and 25 of them had more than 60 years. Objective response was in 94% of patients, with 86% of CR. Progression or relapsed was reported in 34%, and 11% died for progression. At a median follow-up of 38.8 months, median PFS and OS were not reached. Three years PFS and OS were respectively 63% and 90%. Grade 3-4 myelosuppression was limited, with 30% of neutropenia and 26% of thrombocytopenia. The study showed good efficacy and safety of single dose of Zevalin in untreated patients, even in the elderly population.[42]

Recommendations of the Authors: In limited stage, FL radiotherapy alone is the preferred choice. In elderly patients with advanced stage, low tumor burden FL the watch and wait approach is the most appropriate strategy. Treatment is a need in high tumor burden symptomatic FL. The introduction of Rituximab improved OS and PFS, but the optimal chemotherapy to associate remains unsettled, above all in elderly patients, for whom age, comorbidities, and frailty should be considered for clinical decision. R-Bendamustine may be regarded as the first choice, but also CHOP/CVP/FND are suitable alternatives, also in elderly patients.

Maintenance/Consolidation Therapy. After first line therapy, the majority of patients achieve complete remission of the disease, however, most patients relapse. On this basis, many different strategies were studied to delay the relapse and to ameliorate the outcome of these patients, such as maintenance or consolidation treatment.

Rituximab maintenance for 2 years improves PFS (75% versus 58% after 3 years, $p<0.0001$), whereas a shorter maintenance period results in an inferior benefit.[43-44]

As consolidation strategy, radioimmunotherapy with Zevalin demonstrated to prolong PFS after chemotherapy. However, the advantage after rituximab-containing regimens has been not fully evaluated. This option would remain a valid alternative in patients not eligible for high-dose chemotherapy and autologous stem cell transplantation (ASCT) even if its benefit seemed to be inferior in comparison to Rituximab maintenance for 2 years.[45] Indeed a Spanish randomized phase II trial compared consolidation with a single dose of Zevalin (arm A) versus maintenance with Rituximab (arm B) for 2 years in newly diagnosed FL responding to R-CHOP. 146 patients were enrolled (median age 55 yrs), 124 were randomized to induction therapy and 22 patients were excluded for neutropenia or thrombocytopenia, patient decision and unsatisfying response (< PR). 51% received Zevalin and 49% Rituximab. After a median follow-up of 37 months 32 patients relapsed/progressed with a 36-months PFS of 64%

in Zevalin arm and 86% with Rituximab. Number of PR which increased to CR during maintenance were 50% and 46% in arm A, and B respectively. With Zevalin 5 and 6 cases of ≥ 3-grade thrombocytopenia and neutropenia were respectively described, whereas only one case of ≥ 3-grade neutropenia was reported in Rituximab group. In conclusion, maintenance with Rituximab was superior to Zevalin, in term of PFS and toxicity. At present, no sufficient data are available on long-term follow-up.[46]

Focus on the Phase III Trial ML17638.[47] The goal of treatment in elderly patients with FL is to maintain clinical efficacy while minimizing toxicity and preserving the patient's quality of life. The combination of rituximab and fludarabine-based chemotherapy (fludarabine, mitoxantrone, dexamethasone; R-FND) has been shown to be well-tolerated and efficient also in elderly patients.[48] Regardless of induction therapy, rituximab maintenance has been shown to prolong the duration of response in treatment-naive patients as well as in those with relapsed/refractory disease.[49-52] However, none of these trials were designed specifically for elderly patients, and there is little data on maintenance therapy in the elderly.

On these basis the phase III trial ML17638 was designed by the Fondazione Italiana Linfomi, with the aim to evaluate the efficacy and safety of a short rituximab maintenance regimen compared to no further treatment in elderly patients with advanced FL who had responded to a brief first-line treatment regimen consisting of 4 courses of R-FND chemoimmunotherapy followed by 4 weekly doses of rituximab consolidation.[47]

A total of 234 elderly patients affected by treatment-naïve FL were enrolled. It must be noted that median age was 66 years (range 60-75) and patients aged more than 70 years were 23%; 41% of patients had no comorbidities according to CGA score, while 23% of them presented more than 2 concomitant comorbidities. All patients enrolled began a chemoimmunotherapy with 4 monthly courses of R-FND followed by 4 weekly cycles of rituximab consolidation. Of these, 202 responders were randomized to rituximab maintenance (Arm A) once every 2 months for a total of 4 doses or observation (Arm B). Median age in Arms A and B were 66 and 65 years (range: 60-75). After induction and consolidation therapy, the ORR was 86%, with 69% CR. After a 42 month median follow-up from diagnosis, 3y-PFS and 3y-OS were 66% (95%CI:59-72%) and 89% (95%CI:85-93%), respectively. After randomization, 2y- PFS was 81% for rituximab maintenance versus 69% for observation with an HR of 0.63 (95%CI:0.38-1.05, p=0.079), although not statistically significant. Age did not appear to have any significant effect on 3-year PFS. The subgroup of patients below 70 years had a 3-year PFS of 67% (95%CI: 59-73%), compared to 63% (95%CI: 48-75%) for those ≥70 years. There were no differences in 2y-PFS for patients with none, one or two or more comorbidities. **(Figure 2)**. These data suggested that this therapy scheme could be safely administered to older adults and also in those with comorbidities.

No differences between the two arms were detected by OS (9 deaths occurred, 5 in the maintenance and 4 in the observation arms).

As for safety profile of the treatment, the most frequent Grade 3-4 toxicity was neutropenia (25% of treatment courses), with 13 infections. Two toxic deaths (0.8%) occurred during treatment. Overall, the regimen was well-tolerated. In the table (**Table 2)** we reported the overall toxicity, treatment-related and other, according to age and comorbidities reported as events in a total of 1119

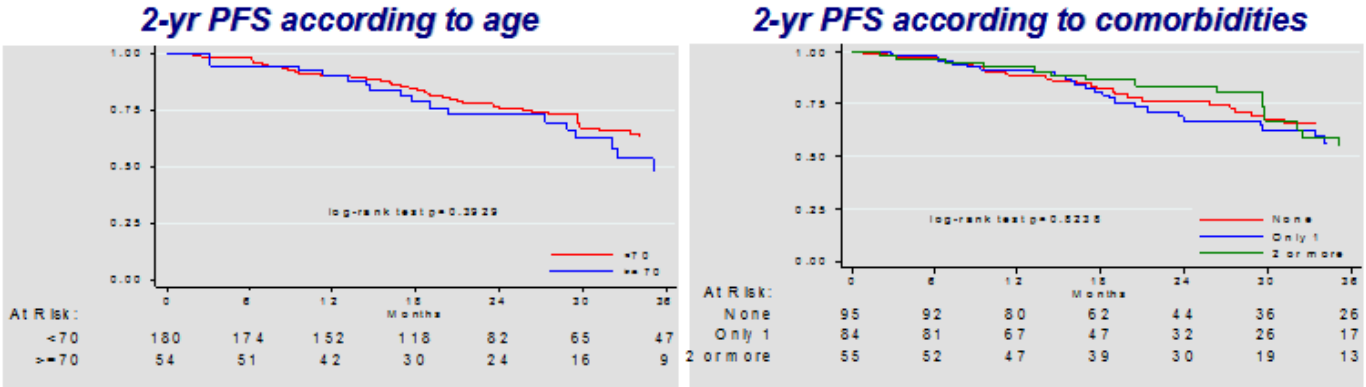

Figure 2. 2years- Progression Free Survival (2y-PFS) according to age and comorbidities in phase III trial ML17638.[47]

Table 2. Overall treatment-related toxicity and toxicity according to age and comorbidities in phase III trial ML17638.[47]

Grade III-IV toxicity evaluated on total administered treatment courses						
	Induction Population (N=234)	**Age**		**Comorbidities**		
		<70 yrs (n=180)	**≥70 yrs (n=54)**	**None (n=94)**	**1 (n=85)**	**≥2 (n=55)**
Neutropenia	280 (25%)	202 (23%)	78 (31%)	115 (26%)	99 (24%)	66 (26%)
Anemia	4 (<1%)	0	4 (2%)	2 (<1%)	2 (<1%)	0
Infections*	13 (1%)	10 (1%)	3 (1%)	9 (2%)	1 (<1%)	3 (1%)
Rituximab infusion reactions	7 (<1%)	5 (<1%)	2 (<1%)	4 (<1%)	3 (<1%)	0
Cardiac	3 (<1%)	1 (<1%)	2 (<1%)	0	1 (<1%)	2 (<1%)
Pulmonary	4 (<1%)	4 (<1%)	0	3 (<1%)	1 (<1%)	0
N° courses administered	**1119**	**864**	**255**	**448**	**415**	**256**

treatment courses administered to 234 patients. The treatment was well-tolerated, and there was the presence of comorbidities, no significant differences were found in the frequency of AEs.

Here we present the results of a recent update of a prolonged follow-up of the ML17638 trial, at 96 months from enrollment and 87 from randomization. We collected data from 127 of 146 patients evaluable.

Long-term follow-up data confirmed the overall favorable outcome, with a 5y-PFS of 57% and a 7y-PFS of 51%. Globally 5y-OS and 7y-OS were 85% and 80% respectively **(Figure 3)**.

The prognostic impact of FLIPI score was confirmed, with a benefit in both PFS and OS in patients with a low-intermediate FLIPI score. The 7y-PFS was 67% in patients with low-intermediate FLIPI vs. 38% in patients with high FLIPI (p<0.001), moreover, 7y-OS was 86% vs. 75% respectively in the two different prognostic groups (p=0.03).

As for maintenance treatment, no differences were shown between maintenance and observation arms, with a 7y-PFS of 55% vs. 52% respectively (p=0.331, HR 0.8).

In a multivariate analysis, male sex, the absence of molecular remission and high-intermediate/high FLIPI score were confirmed as unfavorable prognostic factors, with HR 1.91 (p=0.003), HR 1.7 (p=0.025) and HR 2.51 (p<0.0001) respectively.**(Table 3)**

No differences were identified between the two arms maintenance vs. observation in any subgroup neither in higher FLIPI score patients.

Also in this updated follow-up of the study, the achievement of a negative PCR at the end of treatment (complete molecular remission) was confirmed to be a favorable prognostic factor, predictive of a better outcome, with a 7y-PFS of 58% vs 36% (p=0.084) respectively in patients without or with minimal residual disease. **(Figure 4)**

No differences between the two arms maintenance vs. observation were observed in patients with minimal residual disease (MRD positive) at the end of induction treatment.

As far as toxicities are concerned, 7y-follow up of ML17638 trial showed similar toxicities in both maintenance and observation arm, for infections, cardiac events, and secondary tumors. In particular, 13 secondary malignancies were observed in the maintenance group vs. 16 in patients who underwent observation alone, with a cumulative incidence of 13.9% (95% CI: 6.4 to 21.4) vs. 10.9% (95% CI: 4.4 to 17.4) respectively.

These results underscore the importance of developing tailored therapies for the elderly, exploring the use of brief chemoimmunotherapy regimens beyond the age of 65.

As for maintenance treatment, the lack of statistical significance in our findings may have different causes. First rituximab maintenance may have a small clinical benefit, which could not be demonstrated with the sample size of this study. However, the lack of statistically significant difference is also confirmed at a longer follow-up. Moreover, the maintenance strategy used in the present study was relatively brief compared to

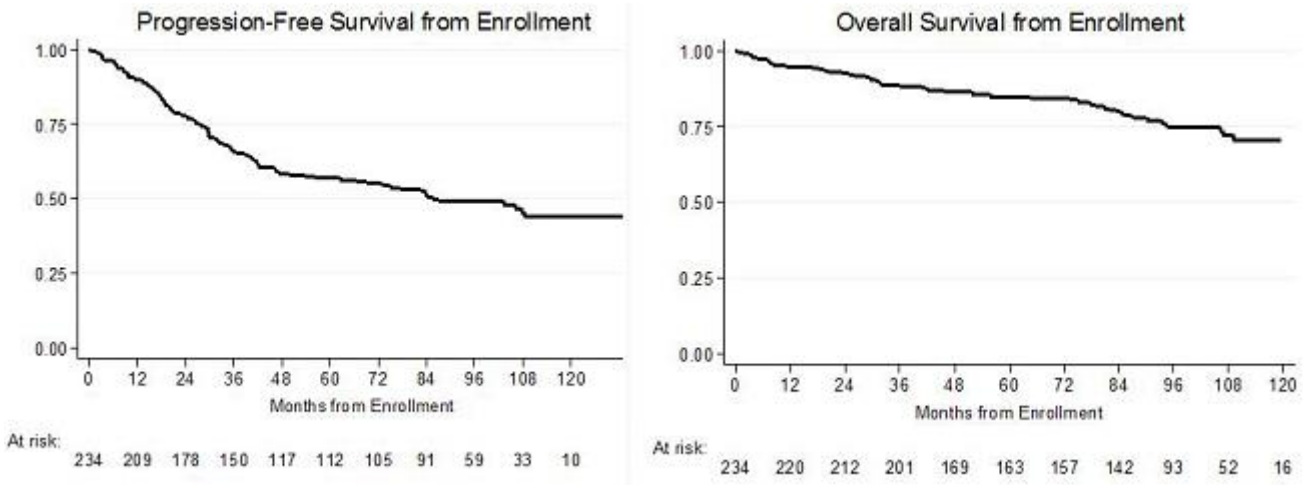

Figure 3. 7 years-Progression Free Survival (7y-PFS) and 7 years-Overall Survival (7y-OS) from recent update of phase III trial ML17638.[47]

Table 3. Cox Proportional Hazards Model effect of prognostic factors on Progression Free Survival (PFS), in phase III trial ML17638.[47]

	HR (95%CI)	**p value**
Maintenance vs Observation	0.8 (0.52-1.22)	0.310
Age (5y increasing)	1.05 (0.82-1.34)	0.707
Male vs female	1.91 (1.24-2.93)	0.003
FLIPI >=3 vs FLIPI _<=2	2.51 (1.61-3.93)	0
Stratum 2 vs Stratum 1	1.7 (1.07-2.7)	0.025
ECOG PS>=1 vs ECOG PS 0	1.5 (0.91-2.48)	0.11

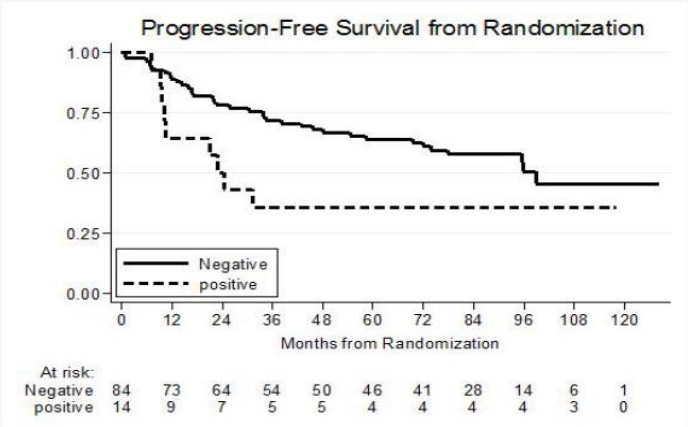

Figure 4. 7 years-Progression Free Survival (7y-PFS) according to minimal residual disease (MRD) in phase III trial ML17638.[47]

"classical" 2-years maintenance, and this may be the cause of the reduced efficacy. Furthermore, in our trial, the results obtained in observation arm were better than expected, and this may be the reason for a smaller absolute difference compared to maintenance arm. Indeed, the lack of differences in PFS in this trial suggests that the benefit of rituximab maintenance could be different on the basis of induction chemotherapy administered. The PRIMA study[43] allowed 3 different induction chemotherapy schemes (R-CHOP, R-CVP and R-FCM (fludarabine, cyclophosphamide, mitoxantrone), but the group of patients who received R-FCM was smaller (only 45 compared to 272 for R-CVP and 885 for R-CHOP) and was the only one which did not seem to benefit from maintenance with rituximab. At the same way, there are no clear data to support an advantage of maintenance with rituximab after bendamustine-based treatment. The MAINTAIN trial compared the results of observation only vs. 2 years vs. 4 years rituximab maintenance in patients with FL in remission after BR induction therapy but failed to demonstrate any differences between the different strategies.[53] In conclusion, the efficacy of rituximab maintenance depends on the clinical contexts and induction therapy.[54]

An assessment of the prognostic value of minimal residual disease (MRD)[20] in patients enrolled in ML17638 trial was done. MRD for the bcl-2/IgH translocation was determined on bone marrow cells in a centralized laboratory belonging

to the Euro-MRD consortium, using qualitative and quantitative polymerase chain reactions (PCRs). Of 234 enrolled patients, 227 (97%) were screened at diagnosis. A molecular marker (MM) was found in 51%. Patients with an MM were monitored at 8 subsequent times. Conversion to PCR negativity predicted better progression-free survival (PFS) at all post-treatment times (eg, end of therapy: 3-year PFS, 72% vs 39%; P <.007). MRD was predictive in both maintenance (83% vs 60%; P <.007) and observation (71% vs 50%; P <.001) groups. PCR positivity at the end of induction was an independent adverse predictor (hazard ratio, 3.1; 95% confidence interval, 1.36-7.07). MRD is one of the most powerful independent outcome predictor in FL patients who receive rituximab-intensive programs, suggesting a need to investigate its value for decision-making, also in an older population.

On the behalf of FIL, based on favorable safety and efficacy profile of Bendamustine and on the results of the ML17638 trial, another study (FLE09 trial) was designed to evaluate the efficacy and the safety profile of a treatment with a combination scheme with rituximab plus bendamustine and mitoxantrone for 4 courses, followed by a consolidation with 4 additional doses of weekly rituximab, in elderly FL patients, extending the upper limit of age to 80 years. Preliminary data from this study are promising, and the publication of the final results of the trial is ongoing.

Recommendations of the Authors: Since relapse is a common event in FL, even in patients achieved complete remission after first-line therapy, maintenance or consolidation therapy is needed.

Maintenance with rituximab for 2 years seems to be an effective strategy and should also be administered in elderly patients. However, the efficacy of rituximab maintenance depends on the clinical contexts and induction therapy used.

Second-Line Therapy and New Drugs. At relapse of disease, it is strongly recommended to obtain a new biopsy to exclude any transformation into an aggressive lymphoma. Targeting the biopsy with a PET scanning may be useful.
As at first presentation, observation is an accepted approach in asymptomatic patients with low tumor burden.

Selection of salvage treatment depends on the efficacy of prior regimens. In early relapse occur (<12-24 months), a non-cross-resistant scheme should be preferred (e.g. bendamustine after CHOP or vice versa). Other options, including fludarabine-based, platinum salts-based or alkylating agents-based regimens, could also be useful, but not applicable in older or unfit patients.

Rituximab should be added if the previous anti-CD20 antibody-containing scheme achieved > 6-12-month duration of remission, while in rituximab-refractory cases, the recently introduced new anti-CD20 antibodies of the second generation, such as obinutuzumab, demonstrated to improve PFS in comparison to chemotherapy alone.[55]

The results of the randomized phase III GADOLIN trial that compared the results of bendamustine alone vs obinutuzumab in association to bendamustine in relapsed/refractory setting in indolent lymphomas have recently been published.[55] 396 patients were enrolled: after a median follow-up of 21.9 months, the PFS was significantly longer with obinutuzumab plus bendamustine (median not reached [95% CI 22·5 months–not estimable]) than with bendamustine monotherapy (14·9 months [12·8–16·6]; hazard ratio 0·55 [95% CI 0·40–0·74]; p=0·0001). Grade 3–5 adverse events occurred in 132 (68%) of 194 patients in the obinutuzumab plus bendamustine group and in 123 (62%) of 198 patients in the bendamustine monotherapy group. This treatment showed to be manageable also in older patients, with acceptable safety profile. Another study that investigated the role of obinutuzumab in association to chemotherapy in relapsed and rituximab refractory FL is GAUDI' trial.[56] Fifty-six patients were enrolled and were randomized to receive obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (G-CHOP; every 3 weeks for 6 to 8 cycles) or obinutuzumab plus fludarabine and cyclophosphamide (G-FC; every 4 weeks for 4 to 6 cycles). Median age was 62.5 years (range 32-75) in G-CHOP arm vs. 61 years (range 45-77) in G-FC group. Treatment responders were eligible for obinutuzumab maintenance every 3 months for up to 2 years. Grade 1/2 infusion-related reactions (IRRs) were the most common treatment-related adverse event. Neutropenia was the most common treatment-related hematologic toxicity. Obinutuzumab plus chemotherapy resulted in 93%

to 96% response rates, with manageable toxicity also in older people, supporting the need for a phase-3 investigation.

Also, radioimmunotherapy may represent an effective therapeutic approach, in particular in elderly patients with comorbidities not appropriate for high dose chemotherapy. Pisani et al.[57] published the results of a retrospective study that investigated the long-term efficacy and safety of a fludarabine, cyclophosphamide and rituximab (FCR) regimen followed by 90Y-ibritumomab tiuxetan consolidation for the treatment of nine patients (median age 63 years, range 46–77), with grades 1 and 2 relapsed FL. After FCR, 7 patients obtained CR and 2 PR; after 90Y-RIT 2 patients in PR converted to CR 12 weeks later. With a median follow-up of 88 months (range 13–104) since 90Y-RIT 3 deaths were not related to lymphoma; all 3 deceased patients obtained CR before 90Y-RIT and died still in CR. The median OS and PFS have not been reached. The most common grade 3 or 4 adverse events were hematologic. The authors concluded that these results confirm the long-term efficacy and safety of 4 cycles of FCR followed by 90Y-RIT in relapsed grades 1 and 2 FL. They suggest that this regimen could be a therapeutic option for this setting of patients, especially at the age of 60–75, who cannot receive high-dose chemotherapy and autologous stem cell transplant, with no unexpected toxicities.

In further relapses, a lot of novel drugs may play a role in monotherapy or in association to other chemotherapy. These new molecules represent an available strategy also in older adults, who are not eligible for high-dose chemotherapy and autologous stem cell transplant programs.

Idelalisib, a phosphatydil-inositol-3 kinase (PI3K) inhibitor, has been registered in double-refractory FL, based on a phase II study, showing on ORR of 54% in this setting of patients.[58] New trials with idelalisib in association to rituximab are ongoing.

Immunomodulatory drugs, such as Lenalidomide, in monotherapy or in association to chemotherapy or monoclonal antibody such as rituximab, demonstrated additional inhibition of the B-cell signaling pathway and had proved activity in phase II studies, but randomized phase III trial are needed to confirm these data.

Fowler et al.[59] presented the results of a phase 2 trial to assess the efficacy and safety of lenalidomide plus rituximab (R2) in patients with untreated, advanced stage indolent non-Hodgkin lymphoma. A total of 110 patients were enrolled, among that 50 FL (whose median age is relatively young: 56 years, range 35-84). ORR for all patients was 90% (95% CI 83–95), with 63% of CR (95% CI 53–72). Of 46 evaluable patients with FL87% achieved CR. The most common grade 3 or 4 adverse events were neutropenia (35%).This study suggested that lenalidomide plus rituximab is well tolerated and highly active as initial treatment for indolent non-Hodgkin lymphoma, and it could be applied in elderly patients not eligible for chemotherapy regimen. An international phase 3 study (RELEVANCE trial) comparing this regimen with chemotherapy in patients with untreated follicular lymphoma is ongoing.

In relapsed/refractory setting, Leonard et al.[60] presenting the results of a randomized phase II trial on 91 patients affected by previously treated FL, whose median age was 63 years (range 34-89). Patients were randomized to receive rituximab (375 mg/m^2 weekly for 4 weeks), lenalidomide (15 mg per day on days 1 to 21, followed by 7 days of rest, in cycle 1 and then 20 mg per day on days 1 to 21, followed by 7 days of rest, in cycles 2 to 12), or a combination therapy rituximab plus lenalidomide (LR). In the lenalidomide and LR arms, grade 3 to 4 adverse events occurred in 58% and 53% of patients. Dose-intensity exceeded 80% in both arms. ORR was 53% (CR 20%) and 76% (CR 39%) for lenalidomide alone and LR, respectively (p=0.029). At the median follow-up of 2.5 years, median TTP was 1.1 year for lenalidomide alone and 2 years for LR (p=0.0023). The combination scheme LR is more active than lenalidomide alone in recurrent FL with similar toxicity, manageable also in elderly patients, warranting further studies.

On behalf of FIL, a randomized phase III multicenter trial to compare a combination of rituximab and lenalidomide vs. rituximab alone as maintenance after R-Bendamustine in relapsed/refractory FL patients (FIL-RENOIR12) is ongoing. There are no age limits for enrollment, and this trial is dedicated mainly to patients over the age of 65 or with comorbidities, who cannot be eligible for high-dose therapy and transplant. Other combinations, such as bortezomib plus rituximab, have shown only a minor benefit compared with antibody monotherapy.

Nivolumab, a monoclonal antibody antiPD1, showed an ORR of 40% in relapsed/refractory FL,[61] supporting the hypothesis of the important role of immunosurveillance in disease control.

Recommendations of the Authors: In early relapsed FL, a non-cross-resistant chemoimmunotherapy scheme should be used. In elderly and frail patients, novel agents (such as new monoclonal antibodies, idelalisib, lenalidomide, and nivolumab), with a good safety profile, should be considered.

Conclusion. Follicular lymphoma is the most common indolent non-Hodgkin lymphoma, typically affects older adults, whose median age at diagnosis is 65 years. FL is considered as an indolent but incurable disease with a median life expectancy of approximately ten years. Randomized clinical trials have demonstrated that the addition of rituximab to standard chemotherapy induction has improved the overall survival. Moreover, maintenance therapy with Rituximab showed improvement of progression-free survival. Despite advances in the treatment of FL, most FL patients remain incurable and, in 10 years, 15% to 28% of cases will transform to an aggressive phenotype, typically diffuse large B-cell lymphoma. New clinical and biological prognostic factors are needed, to tailor therapy better, above all in elderly patients not eligible for aggressive chemotherapy. Some progress were already made with novel agents, but further studies, especially focused on elderly follicular lymphoma patients, with their peculiar characteristics, are needed to define the best-tailored treatment at diagnosis and at the time of relapse in this challenging clinical setting.

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