Randomized Phase III Trial Evaluating Subcutaneous Rituximab for the First-Line Treatment of Low–Tumor Burden Follicular Lymphoma: Results of a LYSA Study

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ABSTRACT

PURPOSE Rituximab improves progression-free survival (PFS) and time to next treatment (TTNT) when compared with the watch and wait strategy for patients with low–tumor burden follicular lymphoma (FL). Prolonged rituximab maintenance did not prolong TTNT, whereas it raises concerns about resources use and patient adhesion. Our aim was then to investigate the use of short rituximab maintenance using the subcutaneous (SC) route in patients with low–tumor burden FL.

METHODS Patients with histologically confirmed CD20$^+$ low–tumor burden FL were randomly assigned to receive either rituximab, 375 mg/m^2 once daily on D1, D8, D15, and D22, intravenous route (IV, control arm), or rituximab, 375 mg/m^2, on day 1 (D1), IV followed by rituximab 1,400 mg total dose, SC once daily on D8, D15, and D22, with maintenance at months 3 (M3), M5, M7, and M9 (experimental arm). The primary end point was PFS. Secondary end points included safety, overall response rates, TTNT, and overall survival (OS).

RESULTS Two hundred two patients with low–tumor burden FL were randomly assigned to the experimental (n = 100) or control arm (n = 102). The primary end point was met: the 4-year PFS was 58.1% (95% CI, 47.5 to 67.4) and 41.2% (95% CI, 30.6 to 51.6) in experimental and control arms, respectively (hazard ratio, 0.585 [0.393 to 0.871]; P = .0076). Complete response (CR) rates were 59.0% (95% CI, 48.7 to 68.7) in the experimental arm and 36.3% (95% CI, 27.0 to 46.4) in the control arm (P = .001). TTNT and OS were not significantly different. CR was associated with longer PFS and TTNT. High rituximab exposure during the first three months was independently associated with higher CR, PFS, and TTNT.

CONCLUSION SC rituximab improves PFS for patients with low–tumor burden FL when used in induction followed by short maintenance. High rituximab exposure during the first 3 months after treatment initiation is, however, the only parameter influencing patient outcomes.

ACCOMPANYING CONTENT

Appendix
Data Supplement
Protocol

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INTRODUCTION

Asymptomatic patients with low–tumor burden follicular lymphoma (FL) represent 20%-30% of patients with FL at diagnosis. For those patients, the watch and wait (W&W) strategy is usually considered as the standard of care.[1] This is justified by a proportion of 19% of patients who did not require any treatment initiation at 10 years[2] and by side effects induced by chemotherapy, the only option available at the time of these reports.[2,3]

However, fear of the patient about cancer, patient requests, and difficulty in organizing W&W make this option difficult. In this context, rituximab demonstrated an acceptable toxicity profile and could overcome anxiety associated with W&W[4,5] without increasing the risk of histologic transformation.[6] Thus, the National LymphoCare Study[7] showed that rituximab is used in daily practice for those patients. Indeed, four-weekly rituximab induction[4] showed a significantly prolonged progression-free survival (PFS) and time to next treatment (TTNT) compared with W&W.

CONTEXT

Key Objective

The role of rituximab maintenance in low–tumor burden follicular lymphoma (FL) remains to be discussed. We designed a randomized trial to evaluate if a short subcutaneous (SC) rituximab maintenance (four infusions) after a SC rituximab induction (first intravenous [IV] and then SC) was superior to standard four weekly IV rituximab infusions.

Knowledge Generated

We demonstrated that short maintenance using SC rituximab increased progression-free survival (PFS) and complete response (CR) rate compared with standard rituximab induction. However, the rituximab exposure observed within the first three months, which was significantly higher in the SC rituximab arm, was independently associated with CR, PFS, and time to next treatment, suggesting that short rituximab maintenance has little impact on outcomes in the context of SC rituximab use during induction.

Relevance *(J.W. Friedberg)*

This study demonstrates that rituximab exposure during the first 3 months of treatment of FL is positively associated with relevant outcomes, and confirms prior efficacy observations of rituximab induction followed by short maintenance.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.

The addition of rituximab maintenance for 2 years increased significantly PFS and TTNT compared with rituximab induction[8] but increased the cost of treatment compared with the rituximab retreatment strategy and led to more treatment discontinuations.[5] Although the benefit of a rituximab induction was significant, these results question the use of prolonged rituximab maintenance. The RESORT study points out that 7 years after treatment initiation, 83% of patients were free of cytotoxic treatment[9] with prolonged maintenance. Similarly, 64.1% and 49.4% of patients receiving rituximab induction with or without prolonged maintenance, respectively, were free of new treatment at 10 years in the UK trial.[8] In the meantime, the SAKK group demonstrated that a short maintenance with four rituximab infusions every two months after rituximab induction[10,11] could also be an approach to maintain response to rituximab.

Rituximab is now available either as a biosimilar, with an intravenous (IV) route of administration, or by subcutaneous (SC) route. The SC rituximab formulation showed an improvement in the patient's experience, a higher rituximab exposure, and optimization of the medical resources compared with the IV route.[12,13] For all these reasons, the LYSA group designed a phase III randomized trial to investigate the use of short rituximab maintenance using SC rituximab in patients with asymptomatic FL.

METHODS

Patients

Patients had to fulfill all the following criteria: histologically confirmed FL CD20$^+$ grade 1, 2, and 3a and bone marrow biopsy (BMB) within 4 months before signing informed consent; no prior therapy; older than 18 years; Ann Arbor stage II-IV; an Eastern Cooperative Oncology Group performance status of 0-2; measurable disease (at least one single node or tumor lesion >1.5 cm); and low tumor burden by the Groupe D'Etude des Lymphomes Folliculaires criteria[3] including lactate dehydrogenase and β2-microglobulin <upper limit of normal.

The Protocol (online only) was approved by an independent ethics committee and the Agence Nationale de Sécurité du Médicament et des Produits de Santé; the study was performed according to the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory requirements. All patients provided written informed consent before participating. The study was registered with ClinicalTrials.gov identifier: NCT02303119 and completed on June 29, 2021.

Study Design and Procedures

Diagnostic biopsies were centrally reviewed (L.X.) to confirm the diagnosis in accordance with WHO guidelines. Patients were randomly assigned (1:1 ratio) to receive the control arm: rituximab 375 mg/m^2 once daily on day 1 (D1), D8, D15, D22 by IV or the experimental arm: rituximab: 375 mg/m^2 at D1 by IV route and 1,400 mg total dose by SC route once daily on D8, D15, and D22, followed by maintenance at month 3 (M3), M5, M7, and M9.

Random assignment was stratified according to Follicular Lymphoma International Prognostic Index (FLIPI) score (<2 v ≥2). Baseline imaging included whole-body computed tomography (CT) scans and positron emission tomography (PET)-CT.

Safety data were collected for up to 30 days after the last infusion (D52 in the control arm, M10 in the experimental arm). Adverse events (AEs) were defined and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events 4.03. Tumor responses were assessed at M3 and M12 by CT scan and at M12 by PET-CT. To confirm a complete response (CR), patients with positive BMB at screening were required to have BMB within 28 days of first achieving CR. CT scan was then performed every 6 months for 2 years and every year for 3 years.

Clinical End Points

The primary end point was the PFS (ie, from the date of inclusion to the date of first documented disease progression, relapse, or death). Secondary end points included response rates at M3 and M12 according to Cheson[14] and Lugano,[15] TTNT (ie, from the date of inclusion to the initiation date of the first documented new lymphoma treatment), and overall survival (OS, ie, from the date of inclusion to the date of death).

Preplanned Exploratory End Points

FcγRIIIA-158VF polymorphism has been described to influence response to rituximab[16] and was determined as previously described.[17] Rituximab serum concentrations were evaluated before rituximab (H0) and 2 hours after the end of rituximab infusion (H2) at D1, D8, D15, and D22, at M3 (H0) for all patients, and at M5, M7, and M9 (H0) in the experimental arm. Concentrations were measured using a validated enzyme-linked immunosorbent assay[18] and were available for 113 patients (control arm: 51, experimental arm: 62). Pharmacokinetics (PK) was assessed using a two-compartment population PK model, with time-varying clearance, and SC absorption described as a first-order rate constant as reported[19] (Data Supplement, online only). Exposure was assessed by computing the AUC using the PK model from the beginning of treatment to M3 ($AUC_{0\text{-}M3}$).

Statistical Analysis

Sample size determination was based on PFS, the primary efficacy end point. To provide 90% power to detect a hazard ratio (HR) of 0.52, corresponding to an increase in the median PFS for the experimental versus control arm[20] with a two-sided alpha (type I error) of 0.05, a total of 102 events from both arms were required, implying 202 patients to be randomly assigned (101 patients in each arm). The analysis was in intent to treat and included all patients randomly assigned regardless of the study drug being received or not received. Patients were analyzed on the basis of the assigned treatment group at the time of random assignment. Response rates were reported as percentages of patients, with 95% CIs. Time-to-event data were presented as Kaplan-Meier plots of time to the first event and as summary tables for fixed time points. Logistic regression models were used to estimate the odd ratios (with 95% CIs) of prognostic factors on response rates (post hoc analyses), and Cox proportional hazards regression models were used to estimate HRs and 95% CIs on time-to-event data. Two different approaches, X-Tile and receiver operating characteristic analysis, were used to define the optimal cutoff with a minimal *P* value of AUC for survival prediction.[21] $AUC_{0\text{-}M3}$ as a time-dependent variable was analyzed using a landmark method with time starting at M3 in both univariable and

TABLE 1. Patient Characteristics

Characteristic	Control Arm (n = 102)	Experimental Arm (n = 100)
Age, median (range)	59.5 (33-80)	59.0 (32-85)
Sex, male/female, No.	45/57	56/44
ECOG 0-1, No. (%)	101 (99)	100 (100)
Ann Arbor stage, No. (%)		
II	24 (24)	17 (17)
III/IV	78 (76)	83 (83)
FLIPI group, No. (%)		
Low (0-1)	44 (43.1)	35 (35)
Intermediate (2-3)	37 (36.3)	44 (44)
High (4-5)	21 (20.6)	21 (21)
FLIPI 2 group, No. (%)		
Low (0)	44 (43.1)	35 (35)
Intermediate (1-2)	58 (56.9)	63 (63)
High (3-5)	0	1 (1)
Histology according to central review, No. (%)		
FL grade 1-2	79 (77.5)	79 (79)
FL grade 3A	11 (10.8)	13 (13)
Unclassified	6 (5.8)	2 (2.0)
3B	1 (1.0)	0
ND or missing data	4 (3.9)	5 (5.0)
Presence of GELF criteria, No.	4	4
SPD, median (range)	1,029.0 (119-4,654)	1,253.5 (96-4,669)
PET-CT, No. (%)	101 (99)	100 (100)
Median SUVmax (range)	9.1 (2.06-31.2)	9.0 (2.30-24.10)
AUC of rituximab, mg/Lxd, median (range)		
$AUC_{0\text{-}M3}$	6,124 (3,237-10,324)	8,648 (5,212-21,381)
Rituximab exposure, mg/m^2, median (range)		
IV	1,500.6 (1,497-1,506)	375 (375-400)
SC	—	9,800 (1,400-9,812)
FCGR3A, No. (%)		
VV	14 (14.9)	12 (13)
VF	45 (47.9)	29 (31.6)
FF	35 (37.2)	51 (55.4)
NA	8	8

Abbreviations: $AUC_{0\text{-}M3}$, AUC from the beginning of treatment to M3; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe D'Etude des Lymphomes Folliculaires; IV, intravenous; NA, not available; ND, not determined; PET, positron emission tomography; SC, subcutaneous; SPD, six largest node; SUVmax, maximum standardized uptake value.

multivariable analyses (post hoc analyses). Analyses were performed using SAS software (version 9.3) and X-Tile (version 3.6.1).

RESULTS

Patient Characteristics

Between February 2015 and June 2018, 202 patients with asymptomatic FL were enrolled and randomly assigned to the experimental (n = 100) or control arm (n = 102). Patient characteristics are summarized in Table 1. Tissue was submitted for central review in 193 patients (96%) and not available for review in nine (4%). Review confirmed FL in 182 patients (90.1%), 158 being FL grade 1 and 2 (78.2%) and 24 grade 3A (11.9%). There were a numerically higher number of women in the control arm (P = .09). According to FLIPI score, 79 (39%), 81 (40%), and 42 (21%) had low- (LR), intermediate- (IR), and high-risk FLIPI score, respectively. One patient had high-risk, and 121 (60%) and 79 (39%) patients had IR and LR FLIPI-2 score, respectively. The median rituximab AUC_{0-M3} was statistically higher in the experimental arm: 8,648 mg/Lxd (5,212-21,381) compared with the control arm, 6,124 mg/Lxd (3,237-10,324, P < .001).

Primary End Point

A total of 18 patients (9%) discontinued the treatment, 11 patients in the experimental arm and seven patients in the control arm (Fig 1). Only four patients discontinued rituximab maintenance. With a median follow-up of 50.2 months (95% CI, 48.3 to 54.5), the primary end point of the study was met (Fig 2A): 4-year PFS of 58.1% (95% CI, 47.5 to 67.4) and 41.2% (95% CI, 30.6 to 51.6) in experimental and control arms, respectively (HR, 0.585; 95% CI, 0.393 to 0.871; P = .008). Univariable analysis demonstrated that the experimental arm, female sex, FLIPI-IR/LR, FLIPI-2-LR, and high AUC_{0-M3} were associated with prolonged PFS (Table 2). While stratified on the treatment arm, a significant difference was observed for PFS between patients with low (≤6,750 mg/Lxd) and high (>6,750 mg/Lxd) AUC_{0-M3} (HR, 0.458; 95% CI, 0.261 to 0.802; P = .005). PFS curves stratified on the treatment arm are provided in Appendix Figure A1 (online only). In multivariable analysis, AUC_{0-M3} was the only parameter significantly associated with PFS; a cutoff of 6,750 mg/Lxd allowed us to separate two groups of patients having a significant different 4-year PFS of 23.7% (95% CI, 8.1 to 43.8) for those having an AUC_{0-M3} ≤ 6,750 mg/Lxd compared with 60.9% (95% CI, 47.3 to 72.1) for those with an AUC_{0-M3} of > 6,750 mg/Lxd (P = .001, Fig 3A). Of note, 45 of

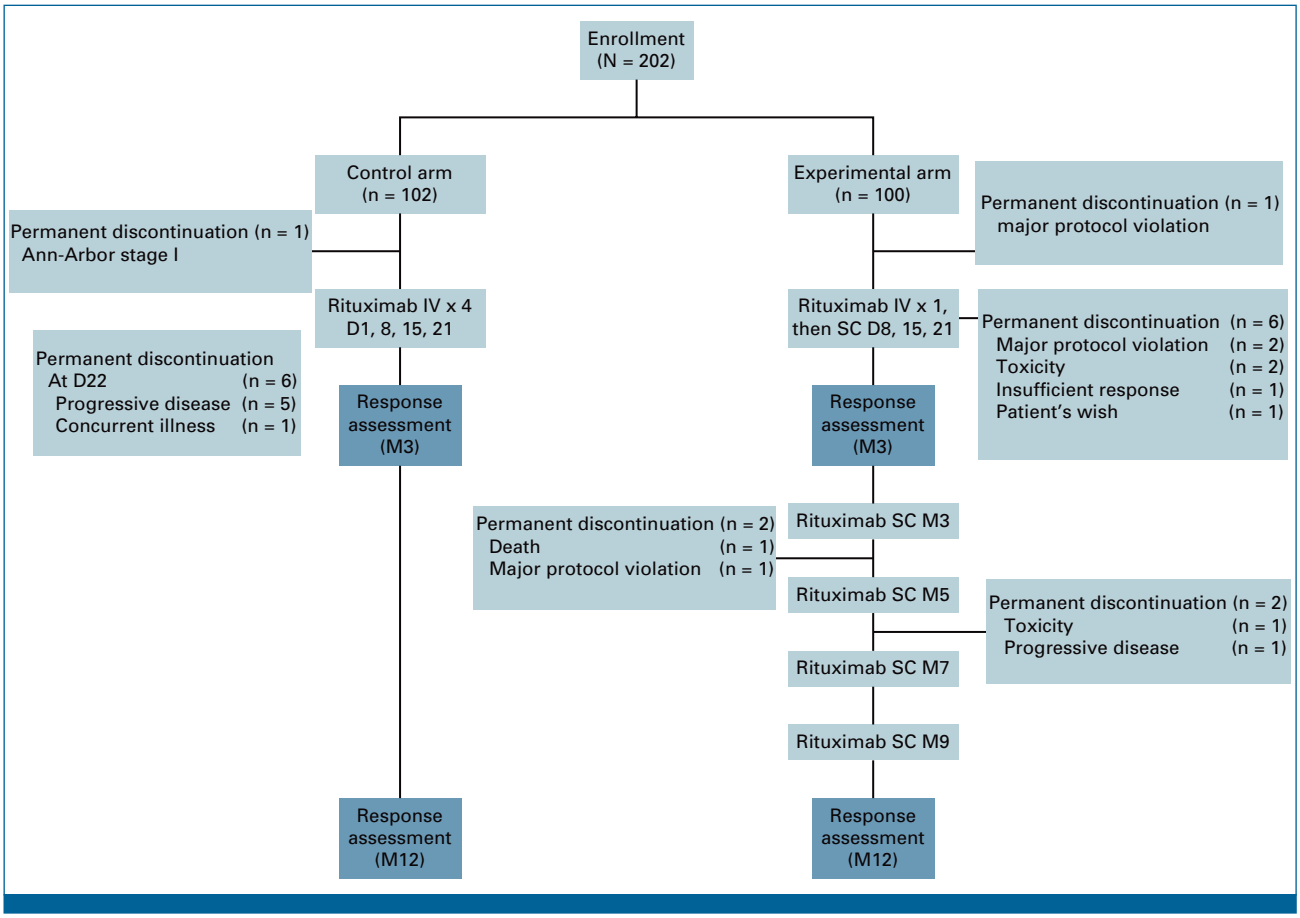

FIG 1. CONSORT diagram. D, day; IV, intravenous; M, month; SC, subcutaneous.

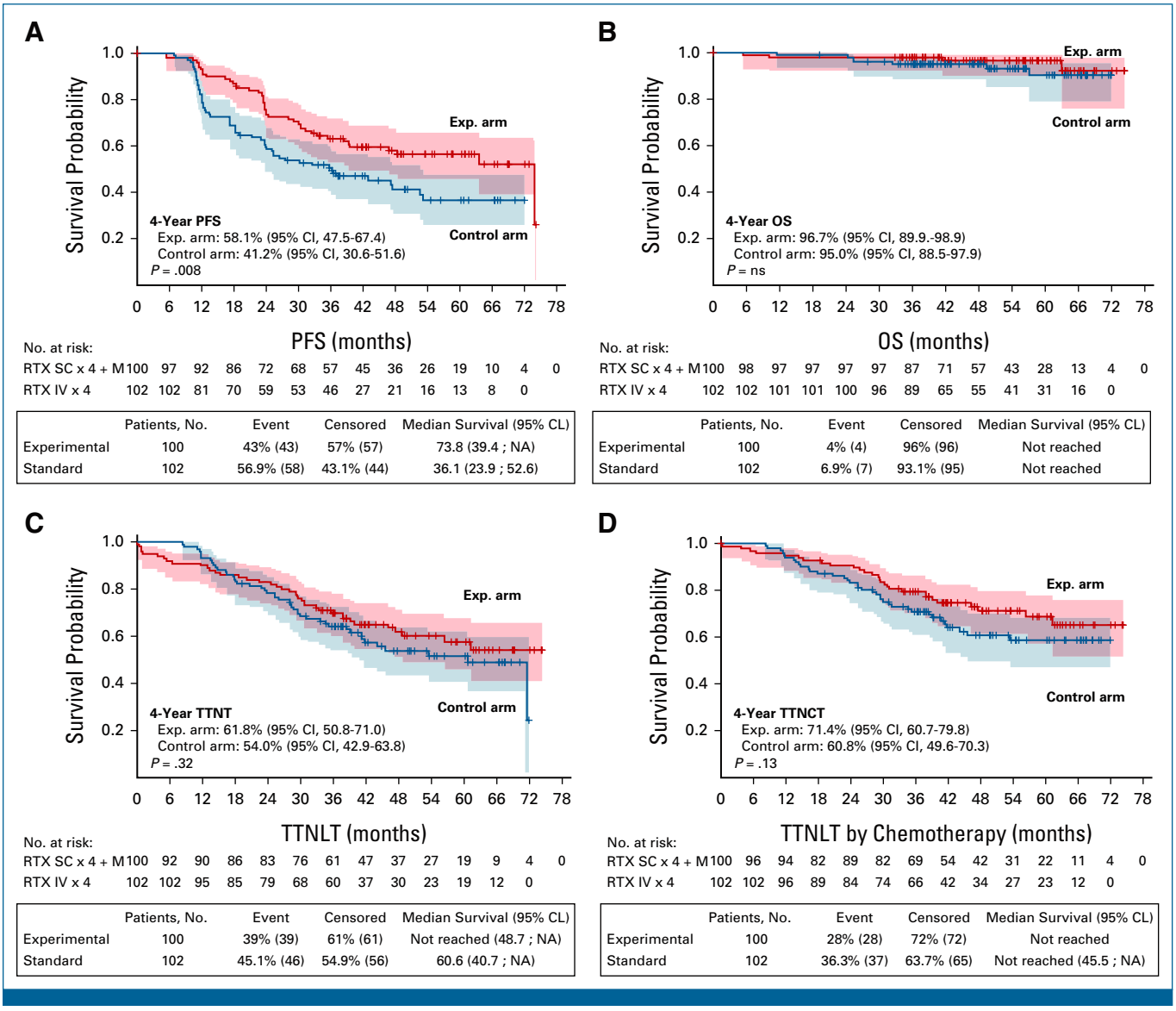

FIG 2. Kaplan-Meier curves of survival: (A) PFS, (B) OS, (C) TTNT, and (D) TTNCT in 202 patients with asymptomatic follicular lymphoma assigned to RTX IV induction or RTX SC induction and maintenance. CL, confidence limit; Exp., experimental; IV, intravenous; ns, nonsignificant; OS, overall survival; PFS, progression-free survival; RTX, rituximab; SC, subcutaneous; TTNCT, time to next chemotherapy treatment; TTNLT, time to next lymphoma treatment; TTNT, time to next treatment.

62 (72%) and 19 of 51 (37%) patients had AUC_{0-M3} > 6,750 mg/Lxd in experimental and control arms, respectively.

Secondary End Points

Toxicities

Before M3, 14 patients in each arm experienced AEs. Seven in each arm had at least one AE ≥ grade 3, for a total of 15 events. AEs ≥ grade 3 observed in more than one patient were lymphopenia (three patients in each arm) and an injection site reaction (three patients in the experimental arm). Eight patients experienced serious AEs: injection site reaction (two patients in the experimental arm, one in the control arm), ulcer (n = 2), arrhythmia (n = 1), skin cancer (n = 1), and cystitis (n = 1). From M3, 17 patients in the experimental arm experienced at least one AE. Five had a total of five AEs ≥ grade 3: benign neoplasm, thyroid cancer, lymphopenia, myocardial ischemia, and hepatitis. Six patients had serious AE: benign neoplasm, skin cancer, thyroid cancer, migraine, peripheral neuropathy, and myocardial ischemia.

Response to Rituximab

According to Cheson criteria,[14] overall response rates (ORRs) at M3 were 80% (95% CI, 70.8 to 87.3) with 29.0% (95% CI, 20.4 to 38.9) CR/complete response unconfirmed (Cru) and 83.3% (95% CI, 74.7 to 90.0) with 38.2% CR/CRu (95% CI, 28.8 to 48.4) in experimental and control arms, respectively (P = .54 and .165 for ORR and CRR, respectively). At M12,

TABLE 2. Prognostic Factor Analyses

Variable	Modality	Univariate			Multivariate		
		HR	95% CI	*P*	HR	95% CI	*P*
PFS							
$AUC_{0\text{-}M3}$	≤6,750 (ref) *v* >6,750	0.427	0.251 to 0.726	.0010	0.428	0.251 to 0.726	.0010
Arm of treatment	Control (ref) *v* Exp.	0.585	0.393 to 0.871	.0080			
Sex	Men (ref) *v* women	0.629	0.422 to 0.937	.0210			
FLIPI-2 (IR *v* LR)	LR (ref) *v* IR	1.519	1,000 to 2.380	.0480			
FLIPI (high-risk *v* IR/LR)	LR/IR *v* high-risk	1.928	1.143 to 3.252	.0140			
TTNT							
$AUC_{0\text{-}M3}$	≤6,200 (ref) *v* >6,200	0.360	0.198 to 0.653	.0005	0.333	0.182 to 0.609	.0004
Sex	Men (ref) *v* women	0.692	0.450 to 1.063	.0910			
Arm of treatment	Control (ref) *v* Exp.	0.806	0.526 to 1.236	.3220			
FLIPI-2	LR (ref) *v* IR	1.592	1.007 to 2.516	.0450	1.938	1.024 to 3.670	.0420

Variable	Modality	Univariate			Multivariate		
		OR	95% CI	*P*	OR	95% CI	*P*
CR M12							
Arm of treatment	Control (ref) *v* Exp.	2.528	1.434 to 4.458	.0014			
FLIPI-2	LR (ref) *v* IR	0.505	0.284 to 0.898	.0200	0.325	0.140 to 0.752	.008
$AUC_{0\text{-}M3}$	≤7,508 *v* >7,508	3.933	1.796 to 8.611	.0006	7.449	1.446 to 38.368	.016

Abbreviations: $AUC_{0\text{-}M3}$, AUC from the beginning of treatment to M3; CR, complete response; Exp., experimental; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; IR, intermediate-risk; LR, low-risk; OR, odds ratio; PFS, progression-free survival; TTNT, time to next treatment.

ORRs were 80% (95% CI, 70.8 to 87.3) with 55.0% (95% CI, 44.7 to 65.0) CR/Cru and 69.6% (95% CI, 59.7 to 78.3) with 46.1% (95% CI, 36.2 to 56.2) CR/Cru in experimental and control arms, respectively (P = .089 and .205 for ORR and CRR, respectively).

According to Lugano criteria including both PET-CT and BMB,[15] ORRs at M12 were 73.0% (95% CI, 63.2 to 81.4) in the experimental arm and 52.0% (95% CI, 41.8 to 62.0) in the control arm (Fig 4; P = .002). CR rates were 59.0% (95% CI, 48.7 to 68.7) in the experimental arm and 36.3% (95% CI, 27.0 to 46.4) in the control arm (P = .001). Univariable analysis demonstrated an association between CR and the experimental arm, FLIPI-2 LR, and $AUC_{0\text{-}M3}$ > 7,508 mg/Lxd (Table 2). Multivariable analysis showed that FLIPI-2 IR was associated with a lower probability of CR (odds ratio [OR], 0.325; 95% CI, 0.140 to 0.752; P = .008), whereas a high $AUC_{0\text{-}M3}$ was significantly associated with a higher CR rate (OR, 7.449; 95% CI, 1.446 to 38.368; P = .016).

Survival and Outcome at First Relapse

Four-year OS was not different according to the treatment arm: 95.0% (95% CI, 88.5 to 97.9) for the control arm and 96.7% (95% CI, 89.9 to 98.9) for the experimental arm (Fig 2B). The lymphoma was the cause of death in only one patient. TTNT and time to next chemotherapy treatment (TTNCT) did not differ (Figs 2C and 2D) with the 4-year TTNCT of 71.4% (95% CI, 60.7 to 79.8) in the experimental arm and 60.8% (95% CI, 49.6 to 70.3) in the control arm (P = .13). In univariable analysis, female sex, experimental arm, FLIPI-2 LR, and high $AUC_{0\text{-}M3}$ were associated with longer TTNT (Table 2). While stratified on the treatment arm, a significant difference was observed for TTNT between patients with low (≤6,200 mg/Lxd) and high (>6,200 mg/Lxd) $AUC_{0\text{-}M3}$ (HR, 0.458; 95% CI, 0.242 to 0.865; P = .014). TTNT curves stratified on the treatment arm are provided in the Data Supplement (Supplemental Figure). FLIPI-2 LR (HR, 1.944; 95% CI, 1.027 to 3.681; P = .041) and high $AUC_{0\text{-}M3}$ (HR, 0.332; 95% CI, 0.182 to 0.608; P = .003) were associated with prolonged TTNT in multivariable analysis (Table 2; Fig 3B).

Ninety-seven patients experienced progression (experimental arm: 42, control arm: 55), and 53 patients (experimental arm: 22, control arm: 31) started treatment at first progression: immunochemotherapy (n = 40), immunotherapy (n = 6), radiotherapy (n = 8), or surgery (n = 1). There was no significant difference in 18-month PFS-2 (ie, progression after a second-line treatment): 66.7% (95% CI, 47.6 to 80.2) and 75% (95% CI, 60.1 to 85.1) for patients included in experimental and control arms, respectively.

Post Hoc Analysis

Because $AUC_{0\text{-}M3}$ was associated with PFS, TTNT, and CR at M12, we analyzed how patient characteristics could influence

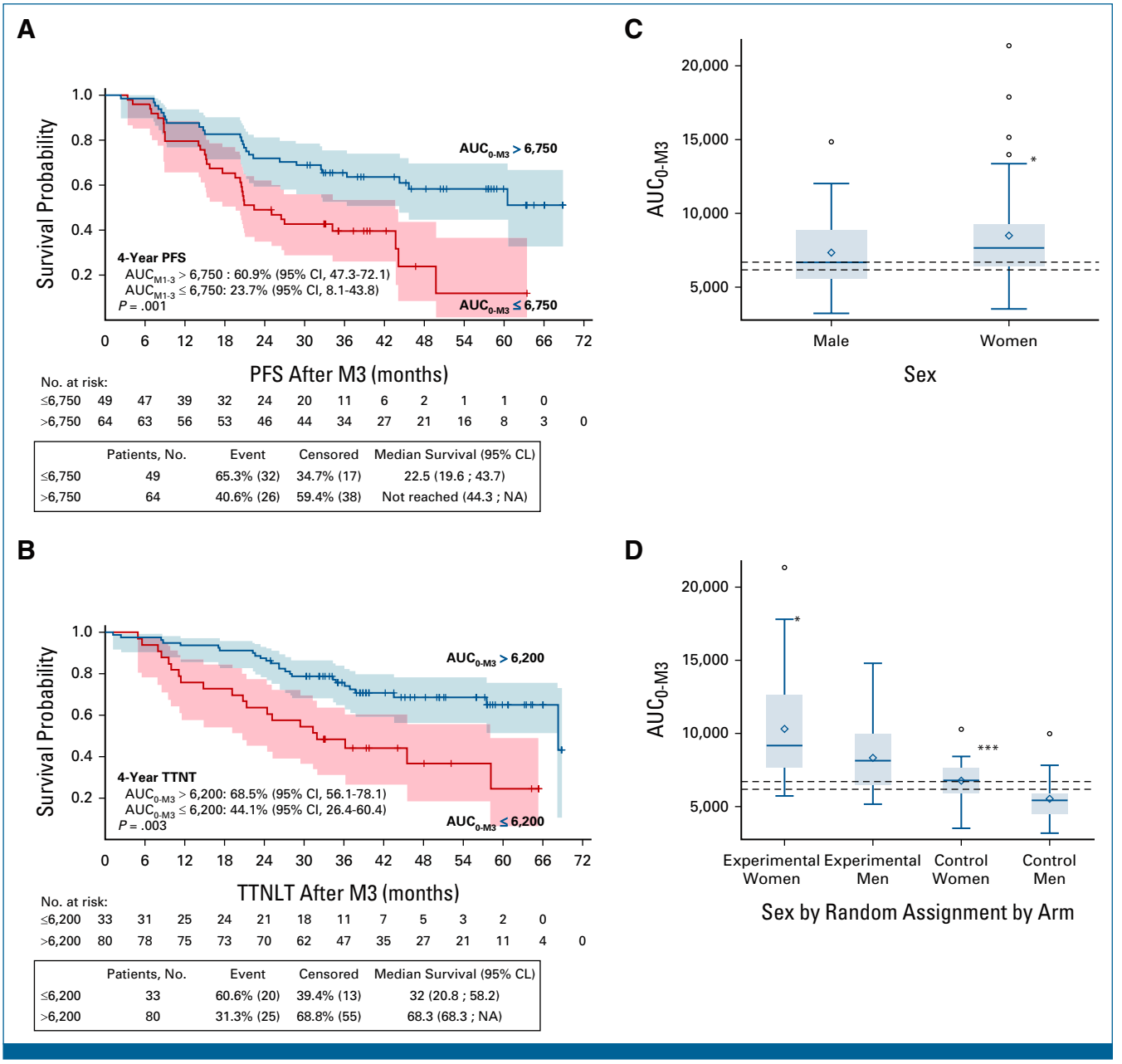

FIG 3. Landmark survival by rituximab $AUC_{0\text{-}M3}$ and factors affecting $AUC_{0\text{-}M3}$. Landmark (A) PFS and (B) TTNT according to rituximab $AUC_{0\text{-}M3}$ in 113 patients. Rituximab $AUC_{0\text{-}M3}$ according to (C) sex and (D) sex and arm. *P = .048 for comparison of $AUC_{0\text{-}M3}$ according to sex, **P = .037 for comparison of $AUC_{0\text{-}M3}$ according to sex in the experimental arm, and ***P = .003 for comparison of $AUC_{0\text{-}M3}$ according to sex in the control arm. Dotted lines represent cutoff of $AUC_{0\text{-}M3}$ significantly associated with higher PFS and TTNT. $AUC_{0\text{-}M3}$, AUC from the beginning of treatment to M3; CL, confidence limit; M, month; PFS, progression-free survival; TTNLT, time to next lymphoma treatment; TTNT, time to next treatment.

$AUC_{0\text{-}M3}$. Female sex was associated with a significantly higher median of $AUC_{0\text{-}M3}$: 7,658.3 mg/Lxd (3,526-21,381) in women versus 7,332.2 mg/Lxd (3,237-14,884) in men (P = .048, Fig 3C). This was observed significantly in both arms (Fig 3D). Patients with a sum of the product of the greatest diameters of six largest nodes (SPD) lower than the median at baseline also had a higher median $AUC_{0\text{-}M3}$, but this association was observed only in the control arm (P = .042). $AUC_{0\text{-}M3}$ was not different according to age, *FCGR3A* polymorphism, FLIPI, FLIPI-2, and Ann Arbor stage.

CR at both M12 (Lugano criteria) and female sex were associated with a prolonged PFS and TTNT in multivariable analysis: the 3-year PFS was 75.7% (95% CI, 64.9 to 83.6) when CR was obtained compared with 35% (95% CI, 23.3 to 46.9) when no CR was reached at M12 (HR, 0.285; 95% CI, 0.175 to 0.465; P < .001; Fig 5A); the 3-year TTNT was 86.8% (95% CI, 77.1 to 92.5) when CR was reached compared with 33.6% (95% CI, 23.8 to 43.7) when no CR was obtained (HR, 0.114; 95% CI, 0.061 to 0.211; P < .001; Fig 5B).

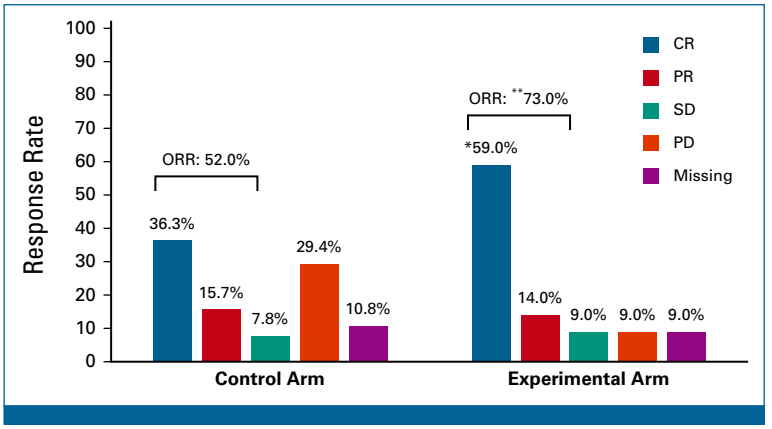

FIG 4. Response at M12 according to Lugano classification. Responses assessed at M12 according to Lugano classification.[13] *$P = .001$ for comparison of CR rates, **$P = .002$ for comparison of odds ratio rates. CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

DISCUSSION

For patients with asymptomatic FL, the question remaining unanswered is whether an optimal rituximab maintenance modality can delay chemotherapy initiation without safety concerns and increasing resources use. Our results show that SC rituximab used for induction and short maintenance increased CR and PFS compared with conventional IV induction. However, the rituximab exposure observed within the first 3 months was independently associated with response, PFS, and TTNT, suggesting that a short rituximab maintenance has a little impact on outcome.

We demonstrated that SC rituximab as induction and maintenance increased significantly PFS compared with rituximab induction with the 4-year PFS of 58.1% and 41.2% in experimental and control arms, respectively. The PFS observed in the control arm appears to be lower than that observed in the UK trial[4] with a 4-year PFS of around 55% with similar IV induction. This could be related to differences in inclusion criteria and more follow-up CT scan in our trial, whereas patient characteristics seem to be similar. The magnitude of the difference in PFS between the two arms in our trial seems like that observed in a similar trial using prolonged maintenance.[4]

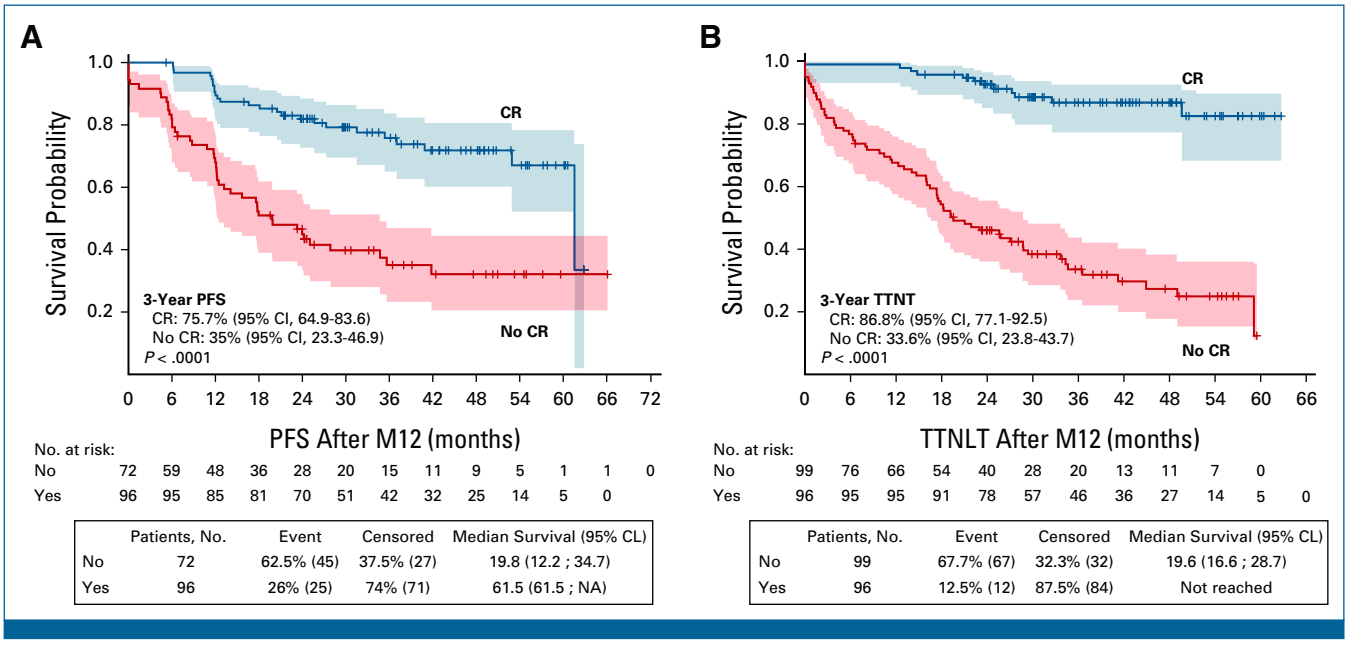

FIG 5. Landmark survival by response status at M12: (A) PFS and (B) TTNT according to response evaluated at M12.[13] CL, confidence limit; CR, complete response; M, month; PFS, progression-free survival; TTNLT, time to next lymphoma treatment; TTNT, time to next treatment.

The lack of effect on OS is mainly explained by the indolent course of FL, highlighted in our study with only one lymphoma-related death. We could not, therefore, confirm the influence of the progression of disease within 2 years on OS.[22] TTNT is an important goal for such patients, and the lack of TTNT improvement is disappointing even if a tendency was observed with TTNCT. This was also found in initial analysis of the UK trial,[4] but its recent update,[8] with a longer follow-up, has shown a significant advantage of prolonged maintenance over no maintenance. Progression is the usual end point in FL and was chosen as the primary end point to calculate the number of patients to be included. Thus, our study might not be powered to demonstrate a difference in TTNT that would have to require consensus on second-line treatment initiation criteria to avoid potential bias for analysis. Similar treatment initiation rates, delay to treatment initiation, and PFS-2 suggest that the policy of retreatment at progression was probably not different according to the treatment arm. The post hoc analysis demonstrated that CR at M12 was associated with a longer PFS and TTNT, with 86.8% of patients in CR being free of treatment 4 years after treatment initiation. CR at the end of treatment could be an interesting end point for physicians and patients to offer individualized follow-up.

The experimental arm is associated with a significantly different rituximab exposure during the first 3 months as demonstrated by higher median $AUC_{0\text{-}M3}$ in the experimental arm. Higher $AUC_{0\text{-}M3}$ was, independent of the treatment arm, associated with higher PFS, TTNT, and CR rate at M12 and seems, therefore, to be an important driver of rituximab efficacy in asymptomatic FL. We have no demonstration that SC route could improve exposure by itself. The cumulative theoretical doses of rituximab for induction were lower in the IV arm (1,500 mg/m²) than in the SC arm (375 mg/m² + 4, 200 mg), which explains probably the difference in the $AUC_{M0\text{-}M3}$ observed according to the arm of treatment. Thus, CR, TTNT, and PFS were related to rituximab exposure during rituximab induction, with the best exposure being obtained more frequently in the experimental arm using higher doses of rituximab. The female sex and low SPD were associated with higher $AUC_{0\text{-}M3}$, and this association was found in both arms with sex and only in the control arm for SPD. The influence of tumor volume on rituximab PK has been demonstrated in a murine model,[23] diffuse large B-cell lymphoma (DLBCL),[24] and FL.[25] Our results suggest that in asymptomatic FL, the higher exposure obtained more frequently in the experimental arm reduced the influence of tumor volume on rituximab efficacy. Female sex has been associated with more favorable rituximab PK in patients with a DLBCL. This was observed especially in elderly women where a slower rituximab clearance led to a longer exposure and better clinical outcome[26,27] but had never been described in FL. The SC route using higher dose of rituximab seems to be the best option to obtain optimal rituximab exposure whatever the sex and SPD are.

Rituximab induces deep and prolonged B-cell depletion that can hamper immune response to SARS-CoV2,[28] increase the risk of severe COVID-19 disease,[29] and prevent immunization.[30] We do not report COVID-19 disease in our cohort of patients, with the last patient being randomly assigned more than 18 months before the SARS-CoV2 wave. The rituximab option must be accompanied by clear and fair information on the potential advantages and risks associated. If the patient agrees, the physician must first ensure that his/her patient is vaccinated and will have access if necessary to antibodies and/or antivirals that reduce significantly COVID-19–related complications.[31]

Our study has, however, several limitations. First, we did not observe a significant impact of maintenance on TTNT, probably because our study was not powered to demonstrate a difference in TTNT. Second, the influence of $AUC_{0\text{-}M3}$ on CR at M12, PFS, and TTNT is observed independently to treatment strongly suggest that rituximab maintenance is not useful if an appropriate dosing of rituximab is use as induction. However, only a randomized study using similar SC rituximab induction followed by maintenance or without maintenance could definitively conclude on that point. Third, the increased exposure observed in the experimental arm is probably more related to the dosage allowed by SC route than by the route itself and we can hypothesize that similar results could be obtained with appropriate dosage using the IV route.

Low–tumor burden FL is an indolent clinical situation where the physician must preserve the patient quality of life and delay chemotherapy use without exposing the patient to significant side effects. Our study clearly demonstrates that rituximab exposure during the first 3 months is an independent parameter influencing response and survival outcomes. In this regard, SC rituximab used as induction allows us to improve rituximab exposure and can be considered by physicians and patients as an optimal option for low–tumor burden FL.

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PRIOR PRESENTATION

Presented in part at the American Society of Clinical Oncology annual meeting, Chicago, IL, June 3, 2022 (abstr 7512).

SUPPORT

LYSARC, the primary funder of the trial, was the sponsor and involved in the management of the study, statistical analyses, and data review. Roche provided rituximab (MabThera) but had no role in study design or data collection, analysis, or interpretation. Roche provided a courtesy review, with comments, of the article before submission, with the authors having final decisions for content reporting in the article.

LYSARC, G.C., and D.P. had access to the raw data. The corresponding author had the final responsibility to submit the article for publication.

CLINICAL TRIAL INFORMATION

NCT02303119 (FLIRT)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

Proposals should be submitted to the study PI and Coordinating Investigator, Guillaume Cartron. If he agrees with the collaboration/sharing, the project should be presented to the LYSA Scientific Committee. If the project is validated by LYSA Scientific Committee, a Data Transfer Agreement compliant with GDPR and French Data Protection laws should be signed. DTA includes data protection rules and responsibilities of each party, data security, and storing information. For more information, please visit https://experts-recherche-lymphome.org/lysarc/ or contact contact@lysarc.org.

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REFERENCES

1. NCCN Guidelines. https://www.nccn.org/guidelines
2. Ardeshna KM, Smith P, Norton A, et al: Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: A randomised controlled trial. Lancet 362:516-522, 2003
3. 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 15:1110-1117, 1997
4. Ardeshna KM, Qian W, Smith P, et al: Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: An open-label randomised phase 3 trial. Lancet Oncol 15:424-435, 2014
5. Kahl BS, Hong F, Williams ME, et al: Rituximab extended schedule or re-treatment trial for low–tumor burden follicular lymphoma: Eastern Cooperative Oncology Group protocol E4402. J Clin Oncol 32:3096-3102, 2014
6. Federico M, Caballero Barrigón MD, Marcheselli L, et al: Rituximab and the risk of transformation of follicular lymphoma: A retrospective pooled analysis. Lancet Haematol 5:e359-e367, 2018
7. Friedberg JW, Taylor MD, Cerhan JR, et al: Follicular lymphoma in the United States: First report of the National LymphoCare Study. J Clin Oncol 27:1202-1208, 2009
8. Northend M, Wilson W, Clifton-Hadley L, et al: Long term follow-up of international randomised phase 3 study of rituximab versus a watch and wait approach for patients with asymptomatic, low tumour burden follicular lymphoma shows rituximab is highly effective at delaying time to new treatment without detrimental impact following next line of therapy. Blood 140:1456-1458, 2022 (suppl 1)
9. Kahl B, Hong F, Jegede Y, et al: Long term follow up of RESORT—Rituximab extended schedule or retreatment trial (E4402). Presented at ASCO annual meeting, 2020 (abst 7512)
10. Martinelli G, Hsu Schmitz SF, Utiger U, et al: Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98. J Clin Oncol 28:4480-4484, 2010
11. Moccia AA, Taverna C, Schär S, et al: Prolonged rituximab maintenance in follicular lymphoma patients: Long-term results of the SAKK 35/03 randomized trial. Blood Adv 4:5951-5957, 2020
12. Salar A, Avivi I, Bittner B, et al: Comparison of subcutaneous versus intravenous administration of rituximab as maintenance treatment for follicular lymphoma: Results from a two-stage, phase IB study. Clin Oncol 32:1782-1791, 2014
13. Rummel M, Kim TM, Aversa F, et al: Preference for subcutaneous or intravenous administration of rituximab among patients with untreated CD20+ diffuse large B-cell lymphoma or follicular lymphoma: Results from a prospective, randomized, open-label, crossover study (PrefMab). Ann Oncol 28:836-842, 2017

14. Cheson BD, Horning SJ, Coiffier B, et al: Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas: NCI-sponsored international working group. J Clin Oncol 17, 1999 (abstr 1244)
15. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol 32:3059-3067, 2014
16. Cartron G, Dacheux L, Salles G, et al: Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcγRIIIa gene. Blood 99:754-758, 2002
17. Dall'Ozzo S, Andres C, Bardos P, et al: Rapid single-step FCGR3A genotyping based on SYBR Green I fluorescence in real-time multiplex allele-specific PCR. J Immunol Methods 277:185-192, 2003
18. Blasco H, Lalmanach G, Godat E, et al: Evaluation of a peptide ELISA for the detection of rituximab in serum. J Immunol Methods 325:127-139, 2007
19. Gibiansky E, Gibiansky L, Chavanne C, et al: Population pharmacokinetic and exposure-response analyses of intravenous and subcutaneous rituximab in patients with chronic lymphocytic leukemia. CPT Pharmacometrics Syst Pharmacol 10:914-927, 2021
20. Colombat P, Brousse N, Salles G, et al: Ritux- imab induction immunotherapy for first-line low- tumor-burden follicular lymphoma: Survival analyses with 7-year follow-up. Ann Oncol 23:2380-2385, 2012
21. Camp RL, Dolled-Filhart M, Rimm DL. X-Tile: A new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res 10:7252-7259, 2004
22. Casulo C, Dixon JG, Le-Rademacher J, et al: Validation of POD24 as a robust early clinical end point of poor survival in FL from 5225 patients on 13 clinical trials. Blood 139:1684-1693, 2022
23. Daydé D, Ternant D, Ohresser M, et al: Tumor burden influences exposure and response to rituximab: Pharmacokinetic-pharmacodynamic modeling using a syngeneic bioluminescent murine model expressing human CD20. Blood 113:3765-3772, 2009
24. Tout M, Casasnovas O, Meignan M, et al: Rituximab exposure is influenced by baseline metabolic tumor volume and predicts outcome of DLBCL patients: A Lymphoma Study Association report. Blood 129:2616-2623, 2017
25. Ternant D, Monjanel H, Venel Y, et al: Nonlinear pharmacokinetics of rituximab in non-Hodgkin lymphomas: A pilot study. Clin Pharmacol 85:2002-2010, 2019
26. Muller C, Murawski N, Wiesen MHJ, et al: The role of sex and weight on rituximab clearance and serum elimination half-life in elderly patients with DLBCL. Blood 119:3276-3284, 2012
27. Pfreundschuh M, Muller C, Zeynalova S, et al: Suboptimal dosing of rituximab in male and female patients with DLBCL. Blood 123:640-646, 2014
28. Thakkar A, Pradhan K, Jindal S, et al: Patterns of seroconversion for SARS-CoV-2 IgG in patients with malignant disease and association with anticancer therapy. Nat Cancer 2:392-399, 2021
29. Passamonti F, Cattaneo C, Arcaini L, et al: Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: A retrospective, multicentre, cohort study. Lancet Haematol 7:e737-e745, 2020
30. Herishanu Y, Avivi I, Aharon A, et al: Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood 137:3165-3173, 2021
31. El Chaer F, Auletta JJ, Chemaly RF: How I treat and prevent COVID-19 in patients with hematologic malignancies and recipients of cellular therapies. Blood 140:673-684, 2022

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Phase III Trial Evaluating Subcutaneous Rituximab for the First-Line Treatment of Low–Tumor Burden Follicular Lymphoma: Results of a LYSA Study

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APPENDIX

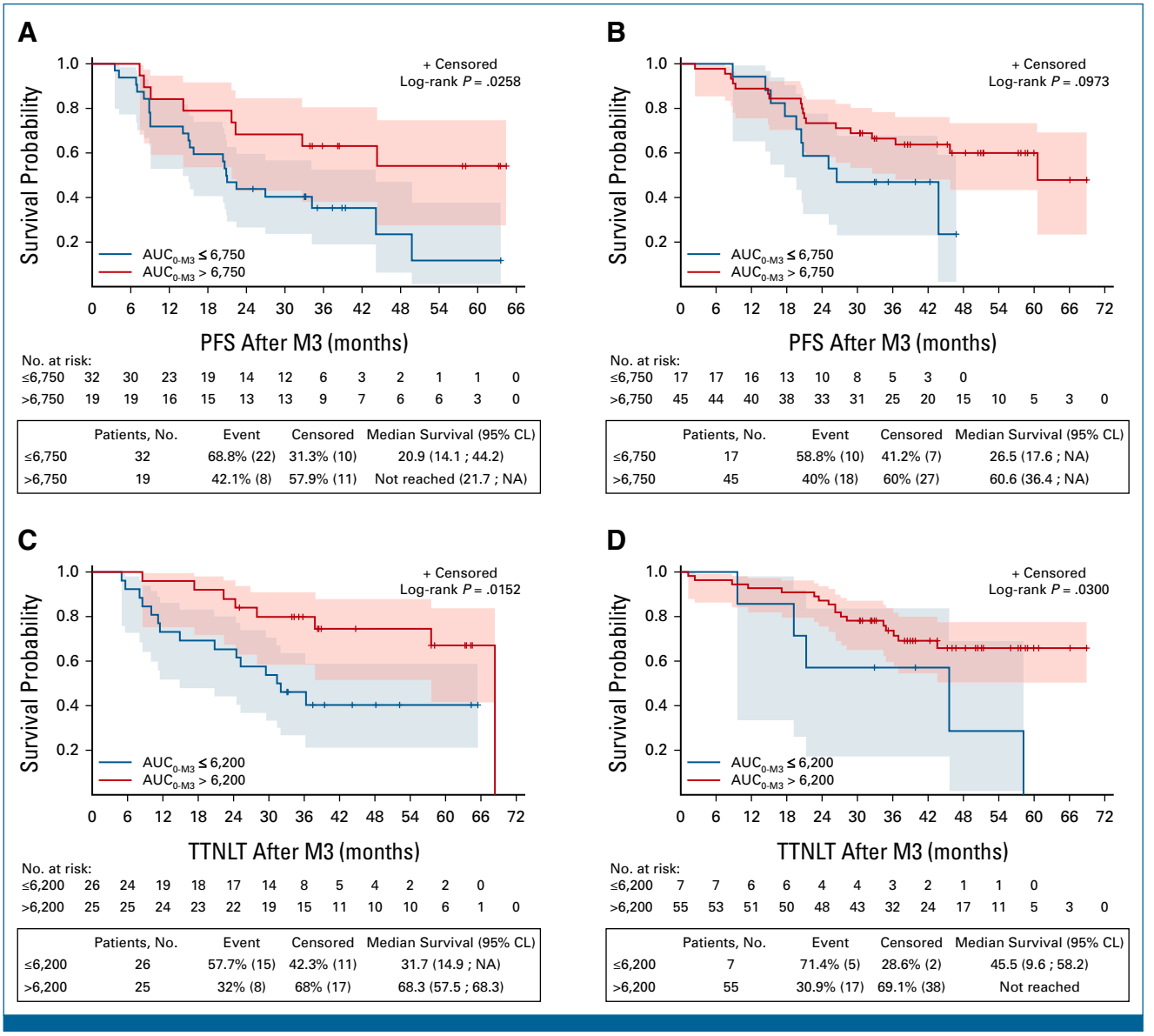

FIG A1. Landmark survival by treatment arm according to $AUC_{0\text{-}M3}$. Landmark (A and B) PFS and (C and D) TTNT by treatment arm for patients with low $AUC_{0\text{-}M3}$ and high $AUC_{0\text{-}M3}$. Low $AUC_{0\text{-}M3}$ and high $AUC_{0\text{-}M3}$ were defined by the appropriate cutoff of 6,750 mg/Lxd and 6,200 mg/Lxd for PFS and TTNT, respectively. $AUC_{0\text{-}M3}$, AUC from the beginning of treatment to M3; CL, confidence limit; M, month; NA, not available; PFS, progression-free survival; TTNLT, time to next lymphoma treatment; TTNT, time to next treatment.