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Guillaume Cartron, Emmanuel Bachy, Hervé Tilly, Nicolas Daguindau, Gian-Matteo Pica, et al.. Randomized Phase III Trial Evaluating Subcutaneous Rituximab for the First-Line Treatment of Low-Tumor Burden Follicular Lymphoma: Results of a LYSA Study. *Journal of Clinical Oncology*, 2023, 41 (19), pp.3523-3533. 10.1200/JCO.22.02327 . hal-04212199

HAL Id: hal-04212199

<https://hal.science/hal-04212199>

Submitted on 16 Oct 2023

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

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Acknowledgments

The authors would like to thank patients, families, caregivers, and investigators who participated in the FLIRT clinical study, the Lymphoma Academic Research Organisation (LYSARC). GC thanks Dr. P. Solal-Céligny, particularly for the passionate discussions on the care of patients with FL, for his review and advices in writing this manuscript.

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Abstract: 270 (≤ 275) words; **body:** 3135 ≤ 3000 words; **tables and figures:** 6 + consort diagram (≤ 6); **references:** 28 (≤ 30)

Prior presentation

Presented at the American Society of Clinical Oncology annual meeting, Chicago, IL, June 3, 2022, Abstract 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, GC, and DP had access to the raw data. The corresponding author had the final responsibility to submit for publication.

Clinical Trial Information

NCT02303119

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 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@lysarc.org.

Context summary

Key Objective

The role of rituximab maintenance in low-tumor burden follicular lymphoma (FL) remains discussed. We designed a randomized trial to evaluate if a short sub-cutaneous (sc.) rituximab maintenance (four infusions) following a sc. rituximab induction (first intravenous and then sc.) was superior to standard four weekly intravenous (iv.) rituximab infusions.

Knowledge Generated

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

ABSTRACT

PURPOSE. Rituximab improves progression-free survival (PFS) and time to next treatment (TTNT) when compared to the “watch and wait” strategy for low-tumor burden follicular lymphoma (FL) patients. 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/m², D1, D8, D15, D22, intravenous route (iv., control arm) or rituximab: 375 mg/m², D1, iv. followed by rituximab 1400 mg total dose, sc., D8, D15, D22, with maintenance at M3, M5, M7, and M9 (experimental arm). The primary endpoint was PFS. Secondary endpoints included safety, overall response rates, TTNT, and overall survival.

RESULTS. 202 patients with low-tumor burden FL were randomly assigned to the experimental (n=100) or control arm (n=102). The primary endpoint was met: 4-year PFS was 58.1% (95% CI:47.5-67.4) and 41.2 % (95% CI:30.6-51.6) in experimental and control arms, respectively (HR 0.585 (0.393-0.871), *P*=0.0076). Complete response (CR) rates were 59.0% (95% CI:48.7-68.7) in experimental arm, 36.3% (95% CI:27.0-46.4) in control arm (*P*=0.001). TTNT and overall survival 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 outcome.

INTRODUCTION

Asymptomatic patients with low-tumor burden follicular lymphoma (FL) represent 20 to 30% of patients with FL at diagnosis. For those patients, the “watch and wait” (W&W) strategy is usually considered as the standard of care¹. This is justified by a proportion of 19% of patients who did not require any treatment initiation at 10 years² 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 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 transformation⁶. Thus, National LymphoCare Study⁷ showed rituximab used in daily practice for those patients. Indeed four-weekly rituximab induction⁴ showed a significant prolonged progression-free survival (PFS) and time to next treatment (TTNT) compared to W&W. The addition of rituximab maintenance for 2 years increased significantly PFS and TTNT compared to rituximab induction⁸ but increased the cost of treatment compared to rituximab re-treatment strategy and led to more treatment discontinuations⁵. Although the benefit of a rituximab induction was significant, these results question the use of prolonged rituximab maintenance. RESORT study points out that 7 years after treatment initiation, 83% of patients were free of cytotoxic treatment⁹ 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 trial⁸. In the meantime, SAKK group demonstrated that a short maintenance with four rituximab infusions every

two months following 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 sub-cutaneous (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 to iv. route^{12,13}. For all these reasons, the LYSA group designed a phase 3 randomized trial to investigate the use of short rituximab maintenance using sc. rituximab in patients with asymptomatic FL.

PATIENTS AND 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, age > 18 years, Ann Arbor stage II-IV, ECOG performance status 0 to 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 (GELF) criteria³ including lactate dehydrogenase and β 2-microglobulin <ULN.

The protocol was approved by an independent ethics committee and the Agence Nationale de Sécurité du Médicament et des Produits de Santé; the study was done according to the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory requirements. All patients gave written informed consent before participating. The study was registered with ClinicalTrials.gov number NCT02303119 and completed on June 29th, 2021.

Study Design and Procedures

Diagnostic biopsies were centrally reviewed (LX) to confirm the diagnosis in accordance with WHO guidelines. Patients were randomly assigned (1:1 ratio) to receive the control arm: rituximab 375 mg/m² at Day-1 (D1), D8, D15, D22 by iv. or the experimental arm: rituximab: 375 mg/m² at D1 by iv. route and 1400 mg total dose by sc. route at D8, D15, and D22, followed by maintenance at months-3 (M3), M5, M7, and M9.

Randomization was stratified according to Follicular Lymphoma International Prognostic Index (FLIPI) score (< 2 vs ≥ 2). Baseline imaging included whole body CT-scans and positron emission tomography-computed 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 NCI-CTCAE 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 Endpoints

The primary endpoint was the PFS (*i.e.*, from the date of inclusion to the date of first documented disease progression, relapse, or death). Secondary endpoints included response rates at M3 and M12 according to Cheson¹⁴ and Lugano¹⁵, TTNT (*i.e.* from the date of inclusion to the initiation date of the first documented new lymphoma treatment), and overall survival (OS, *i.e.* from the date of inclusion to the date of death).

Pre-planned Exploratory Endpoints

Fc γ RIIIA-158VF polymorphism has been described to influence response to rituximab¹⁶ and was determined as previously described¹⁷. Rituximab serum concentrations were evaluated before rituximab (H0) and 2 hours after the end of rituximab infusion (H2) at D1, D8, D15, D22, at M3 (H0) for all patients and at M5, M7, M9 (H0) in the experimental arm. Concentrations were measured using a validated enzyme-linked immunosorbent assay¹⁸ 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 reported¹⁹ (see Supplemental Methods). Exposure was assessed by computing the area under the concentration-time curve (AUC) using the PK model from the beginning of treatment to M3 (AUC_{0-M3}).

Statistical analysis

Sample size determination was based on PFS, the primary efficacy endpoint. To provide 90% power to detect a Hazard Ratio (HR) of 0.52, corresponding to an increase of the median PFS for the experimental *versus* control arm²⁰ with two-sided alpha (type I error) of 0.05, a total of 102 events from both arms was required implying 202 patients to be randomized (101 patients in each arm). The analysis was in intent to treat and included all patients randomized regardless of the study drug being received or not. Patients were analyzed based on the assigned treatment group at the time of randomization. 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 hazard ratios and 95% CIs on time-to-event data. Two different approaches, X-Tile and ROC analysis were used to define the optimal cutoff with a minimal p-value of AUC for survival prediction²¹. AUC_{0-M3} as time-dependent variable was analyzed with a landmark method with time starting at M3 in both univariable and multivariable analysis (post-hoc analyses). Analyses were done with 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 for 9 (4%). Review confirmed FL in 182 patients (90.1%), 158 being FL grade 1, 2 (78.2%), 24 grade 3A (11.9%). There was a numerically higher number of women in the control arm ($P=0.09$). According to FLIPI score, 79 (39%), 81 (40%) and 42 (21%) had low- (LR), intermediate- (IR) and high-risk (HR) FLIPI score, respectively. One patient had HR, and 121 (60%) and 79 (39%) of patients had IR and LR FLIPI-2 score, respectively. The median rituximab AUC_{0-M3} was statistically higher in the experimental arm: 8648 mg/Lxd (5212-21381) compared to the control arm, 6124 mg/Lxd (3237-10324, $P<0.001$).

Primary Endpoint

A total of 18 patients (9%) discontinued the treatment, 11 patients in the experimental arm, and 7 patients in the control arm (Figure 1). Only four patients discontinued rituximab maintenance. With a median follow-up of 50.2 months (95%IC:48.3-54.5), the primary endpoint of the study was met (Figure 2A.): 4-year PFS of 58.1% (95%CI:47.5-67.4) and 41.2% (95%CI:30.6-51.6) in experimental and control arms, respectively (HR:0.585;0.393-0.871), $P=0.008$). Univariable analysis demonstrated that the experimental arm, female gender, 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 (≤ 6750 mg/Lxd) and (high >6750 mg/Lxd) AUC_{0-M3} (HR:0.458; 95%CI:0.261-0.802, $P=0.005$). PFS curves stratified on the treatment arm are provided in Appendix Figure 1. In multivariable analysis, AUC_{0-M3} was the only parameter significantly associated with PFS; a cut-off of 6750 mg/Lxd allowed to separate two groups of patients having a significant different 4-year PFS of 23.7% (95%IC:8.1-43.8) for those having an $AUC_{0-M3} \leq 6750$ mg/Lxd compared to 60.9% (95%IC:47.3-72.1) for those with an $AUC_{0-M3} > 6750$ mg/Lxd ($P=0.001$, Figure 3A). Of note, 45/62 (72%) and 19/51 (37%) patients had $AUC_{0-M3} > 6750$ mg/Lxd in experimental and control arms, respectively.

Secondary Endpoints

Toxicities

Before M3, 14 patients in each arm experienced AEs. Seven in each arm had at least one AE \geq grade 3, for a total of 15 events. AEs \geq grade 3 observed in more than one patient were lymphopenia (3 patients in each arm) and an injection site reaction (3 patients in the experimental arm). Eight patients experienced serious AE: injection site reaction (2 patients in experimental arm, one in control arm), ulcer (n=2), arrhythmia

(n=1), skin cancer (n=1), cystitis (n=1). From M3, 17 patients in the experimental arm experienced at least one AE. Five had a total of 5 AE \geq 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 criteria¹⁴, overall response rates (ORR) at M3 were 80% (95%CI:70.8-87.3) with 29.0% (95%CI:20.4-38.9) CR/Cru and 83.3% (95%CI:74.7-90.0) with 38.2% CR/CRu (95%CI:28.8-48.4) in experimental and control arms, respectively ($P=0.54$ and 0.165 for ORR and CRR, respectively). At M12, ORR were 80% (95%CI:70.8-87.3) with 55.0% (95%CI:44.7-65.0) CR/Cru and 69.6% (95%CI:59.7-78.3) with 46.1% (95%CI:36.2-56.2) CR/Cru in experimental and control arms, respectively ($P=0.089$ and 0.205 for ORR and CRR, respectively).

According to Lugano criteria including both PET-CT and BMB¹⁵, ORR at M12 were 73.0% (95%CI:63.2-81.4) in experimental arm and 52.0% (95% CI: 41.8-62.0) in control arm (Figure 4.) ($P=0.002$). CR rates were 59.0% (95%CI:48.7-68.7) in experimental arm and 36.3% (95%CI:27.0-46.4) in control arm ($P=0.001$). Univariable analysis demonstrated an association between CR and the experimental arm, FLIPI-2 LR, and $AUC_{0-M3} > 7508$ mg/Lxd (Table 2.). Multivariable analysis showed that FLIPI-2 IR was associated with a lower probability of CR (OR: 0.325, 95%CI:0.140-0.752, $P=0.008$) whereas a high AUC_{0-M3} was significantly associated with a higher CR rate (OR:7.449, 95%CI:1.446-38.368, $P=0.016$).

Survival and Outcome at First Relapse

4-year OS was not different according to treatment arm: 95.0% (95%CI:88.5-97.9) for control arm, 96.7% (95%CI: 89.9-98.9) for experimental arm (Figure 2B). The lymphoma was the cause of death in only one patient. TTNT and time to next chemotherapy treatment (TTNCT) did not differ (Figure 2C, 2D) with 4-year TTNCT of 71.4% (95%CI:60.7-79.8) in the experimental arm and 60.8 % (95%CI:49.6-70.3) in the control arm ($P=0.13$). In univariable analysis, female gender, experimental arm, FLIPI-2 LR, and high AUC_{0-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 (≤ 6200 mg/Lxd) and (high >6200 mg/Lxd) AUC_{0-M3} (HR:0.458; 95%CI:0.242-0.865, $P=0.014$). TTNT curves stratified on the treatment arm are provides in Appendix Figure 1. FLIPI-2 LR (HR 1.944; CI95%:1.027-3.681, $P=0.041$) and high AUC_{0-M3} (HR:0.332; 95%CI:0.182-0.608, $P=0.003$) were associated with prolonged TTNT in multivariable analysis (Table 2., Figure 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), radiation-therapy (n=8) or surgery (n=1). There was no significant difference in 18 months-PFS-2 (i.e progression after a second line treatment): 66.7% (95%IC:47.6-80.2) and 75% (95%IC:60.1-85.1) for patients included in experimental and control arms, respectively.

Post-hoc Analysis

Because AUC_{0-M3} was associated with PFS, TTNT, and CR at M12, we analyzed how patient' characteristics could influence AUC_{0-M3} . Female gender was associated with a significantly higher median of AUC_{0-M3} : 7658.3 mg/Lxd (3526-21381) in women versus 7332.2 mg/Lxd (3237-14884) in men ($P=0.048$, Figure 3C). This was observed

significantly in both arms (Figure 3D). Patients with a sum of the product of the greatest diameters of 6 largest nodes (SPD) lower than the median at baseline had also a higher median AUC_{0-M3} , but this association was observed only in the control arm ($P=0.042$). AUC_{0-M3} was not different according to age, *FCGR3A* polymorphism, FLIPI, FLIPI-2, and Ann Arbor stage.

CR at M12 (Lugano criteria) and female gender were both associated with a prolonged PFS and TTNT in multivariable analysis: 3-year PFS was 75.7% (95%CI:64.9-83.6) when CR was obtained compared to 35% (95%CI:23.3-46.9) when no CR was reached at M12 (HR:0.285; 95%CI: 0.175-0.465, $P<0.001$, Figure 5A); 3-year TTNT were 86.8% (95%CI:77.1-92.5) when CR was reached compared to 33.6% (95%CI:23.8-43.7) when no CR was obtained (HR:0.114; 95%CI:0.061-0.211, $P<0.001$, Figure 5B).

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 to conventional iv induction. However, the rituximab exposure observed within the first three 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 to rituximab induction with a 4-year PFS of 58.1% and 41.2% in experimental and control arms, respectively. The PFS observed in the control arm appears lower than that observed in the UK trial⁴ with a 4-year PFS 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 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 maintenance⁴.

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 (POD24) on OS²². 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 trial⁴ but its recent update⁸, with a longer follow-up, has shown a significant advantage of prolonged maintenance over no maintenance. Progression is the usual endpoint in FL and was chosen as the primary endpoint 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 re-treatment 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; 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 endpoint for physicians and patients to offer individualized follow-up.

The experimental arm is associated with a significant different rituximab exposure during the first three months as demonstrated by higher median AUC_{0-M3} in experimental arm. Higher AUC_{0-M3} was, independently of the treatment arm, associated with higher PFS, TTNT, and CR rate at M12, and seems therefore 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 iv. arm (1500 mg/m²) than in sc. arm (375 mg/m² + 4200 mg) explain probably the difference of the AUC_{M0-M3} observed according to the arm of treatment. Thus, CR, TTNT, and PFS were related to rituximab exposure during rituximab induction, the best exposure being obtained more frequently in experimental arm using higher doses of rituximab. The female gender and low SPD were associated with higher AUC_{0-M3}, this association was found in both arms with gender and only in the control arm for SPD. The influence of tumor volume on rituximab PK has been demonstrated in a murine model²³, diffuse large B-cell lymphoma (DLBCL)²⁴ and FL²⁵. Our results suggest that in asymptomatic FL, the higher exposure obtained more frequently in experimental arm reduced the influence of tumor volume on rituximab efficacy. Female gender 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 the best option to obtain optimal rituximab exposure whatever the gender and SPD. Rituximab induces deep and prolonged B-cell depletion that can hamper immune response to SARS-CoV2²⁸, increase the risk of severe COVID-19²⁹ and prevent immunization³⁰. We do not report COVID-19 infection in our cohort of patients, the last patient being randomized 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 complications³¹.

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-M3} on CR at M12, PFS, and TTNT 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 not 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 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 allow to improve rituximab exposure and can be considered by physicians and patients as an optimal option for low-tumor burden FL.

CONTRIBUTORS

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Provision of study materials or patients: All authors

Collection and assembly data: Guillaume Cartron, David Ternant, Karine Tarte, Delphine Pranger.

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Manuscript writing: All authors

Final approval of manuscript: All authors

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Table 1. Patient Characteristics

	Control arm (n=102)	Experimental arm (n=100)
Age (median, range)	59.5 (33-80)	59.0 (32-85)
Sex M/W	45/57	56/44
ECOG 0-1 (n, %)	101 (99)	100 (100)
Ann Arbor stage (n, %)		
- II	24 (24)	17 (17)
- III/IV	78 (76)	83 (83)
FLIPI group (n, %)		
- 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 (n, %)		
- 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 (n, %)		
- 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 (n)	4	4
SPD, median (range)	1029.0 (119-4654)	1253.5 (96-4669)
TEP-CT (n, %)	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-M3}	6124 (3237-10324)	8648 (5212-21381)
Rituximab exposure (mg/m², median, range)		
- IV	1500.6 (1497-1506)	375 (375-400)
- SC	-	9800 (1400-9812)
FCGR3A (n,%)		
- VV	14 (14.9)	12 (13)
- VF	45 (47.9)	29 (31.6)
- FF	35 (37.2)	51 (55.4)
- NA	8	8

Table 2. Prognostic Factors Analysis

Variable	Modality	Univariate			Multivariate		
		HR	95% CI	P	HR	95% CI	P
PFS							
AUC _{0-M3}	≤ 6750 (ref) vs > 6750	0.427	0.251-0.726	0.001	0.428	0.251-0.726	0.001
Arm of treatment	Control (ref) vs exp.	0.585	0.393-0.871	0.008			
Sex	Men (ref) vs women	0.629	0.422-0.937	0.021			
FLIPI-2 (IR vs LR)	LR (ref) vs IR	1.519	1.000-2.380	0.048			
FLIPI (HR vs IR/LR)	LR/IR vs HR	1.928	1.143-3.252	0.014			
TTNT							
AUC _{0-M3}	≤ 6200 (ref) vs > 6200	0.360	0.198-0.653	0.0005	0.333	0.182-0.609	0.0004
Sex	Men (ref) vs women	0.692	0.450-1.063	0.091			
Arm of treatment	Control (ref) vs exp.	0.806	0.526-1.236	0.322			
FLIPI-2	LR (ref) vs IR	1.592	1.007-2.516	0.045	1.938	1.024-3.670	0.042
CR M12							
Arm of treatment	Control (ref) vs exp.	2.528	1.434-4.458	0.0014			
FLIPI-2	LR (ref) vs IR	0.505	0.284-0.898	0.02	0.325	0.140-0.752	0.008
AUC _{0-M3}	≤ 7508 vs > 7508	3.933	1.796-8.611	0.0006	7.449	1.446-38.368	0.016

FIGURE LEGENDS

Figure 1. CONSORT Diagram

Figure 2. Kaplan Meier Curves of Survival

Progression-free survival (A), overall survival (B), time to next treatment (C) and time to next cytotoxic treatment in 202 patients with asymptomatic follicular lymphoma assigned to rituximab iv. induction or rituximab sc. induction and maintenance.

Figure 3. Landmark Survival by Rituximab AUC_{0-M3} and Factors Affecting AUC_{0-M3}

Landmark progression-free survival (A) and time to next treatment (B) according to rituximab AUC_{0-M3} in 113 patients. Rituximab AUC_{0-M3} according to sex (C) and sex and arm (D). $^{\&}P=0.048$ for comparison of AUC_{0-M3} according to gender, $^*P=0.037$ for comparison of AUC_{0-M3} according to gender in experimental arm, $^{\#}P=0.003$ for comparison of AUC_{0-M3} according to gender in control arm. Dotted lines represent cut-off of AUC_{0-M3} significantly associated with higher PFS and TTNT.

Figure 4. Response at M12 According to Lugano Classification

Responses assessed at M12 according to Lugano Classification¹³. CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease. $^*P=0.001$ for comparison of CR rates, $^{\#}P=0.002$ for comparison of OR rates.

Figure 5. Landmark Survival by Response Status at M12

Progression-free survival (A) and time to next treatment (B) according to response evaluated at M12¹³. CR: complete response.

Supplemental Figure. Landmark Survival by treatment arm according to AUC_{0-M3}.
M3.

Landmark progression-free survival (A, B) and time to next treatment (C, D) by treatment arm for patients with low AUC_{0-M3} and high AUC_{0-M3}. Low and high AUC_{0-M3} were defined by appropriate cut-off of 6750 mg/Lxd and 6200 mg/Lxd for progression-free survival and time to next treatment, respectively.

Figure 1. CONSORT Diagram

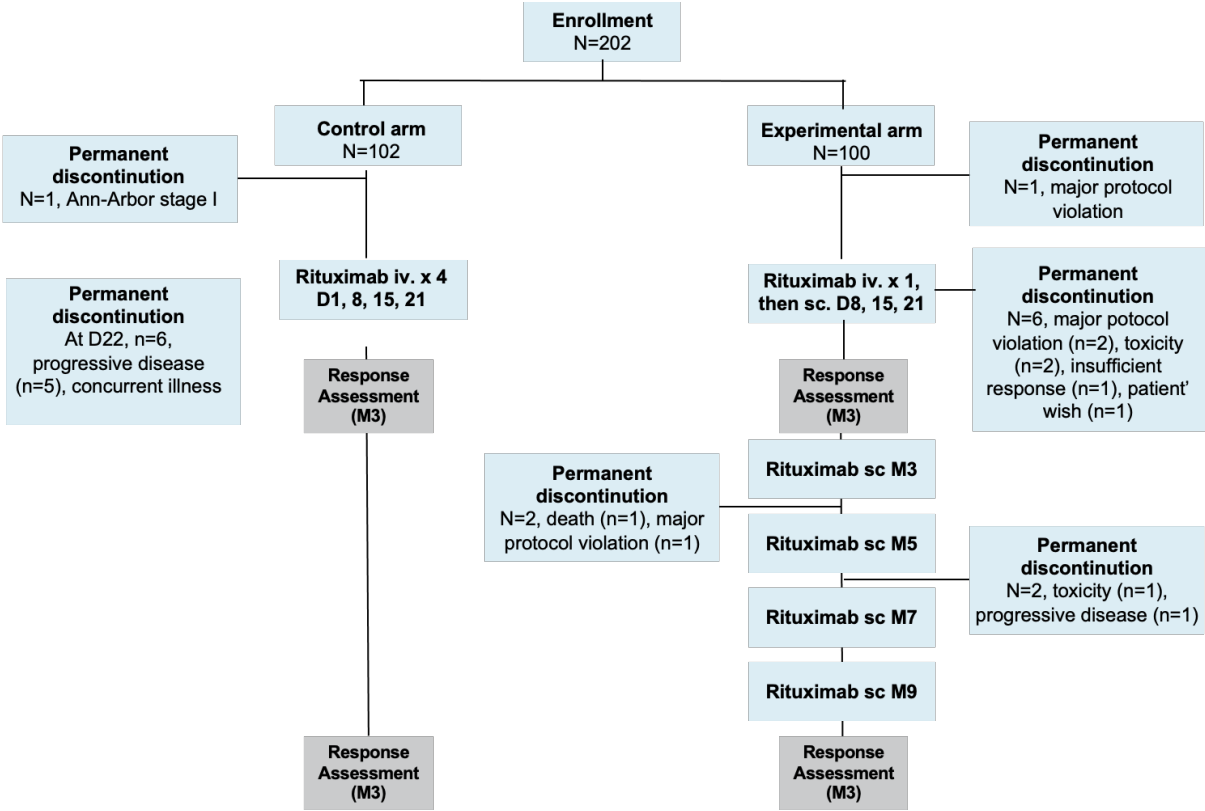


Figure 2. Kaplan Meier Curves of Survival

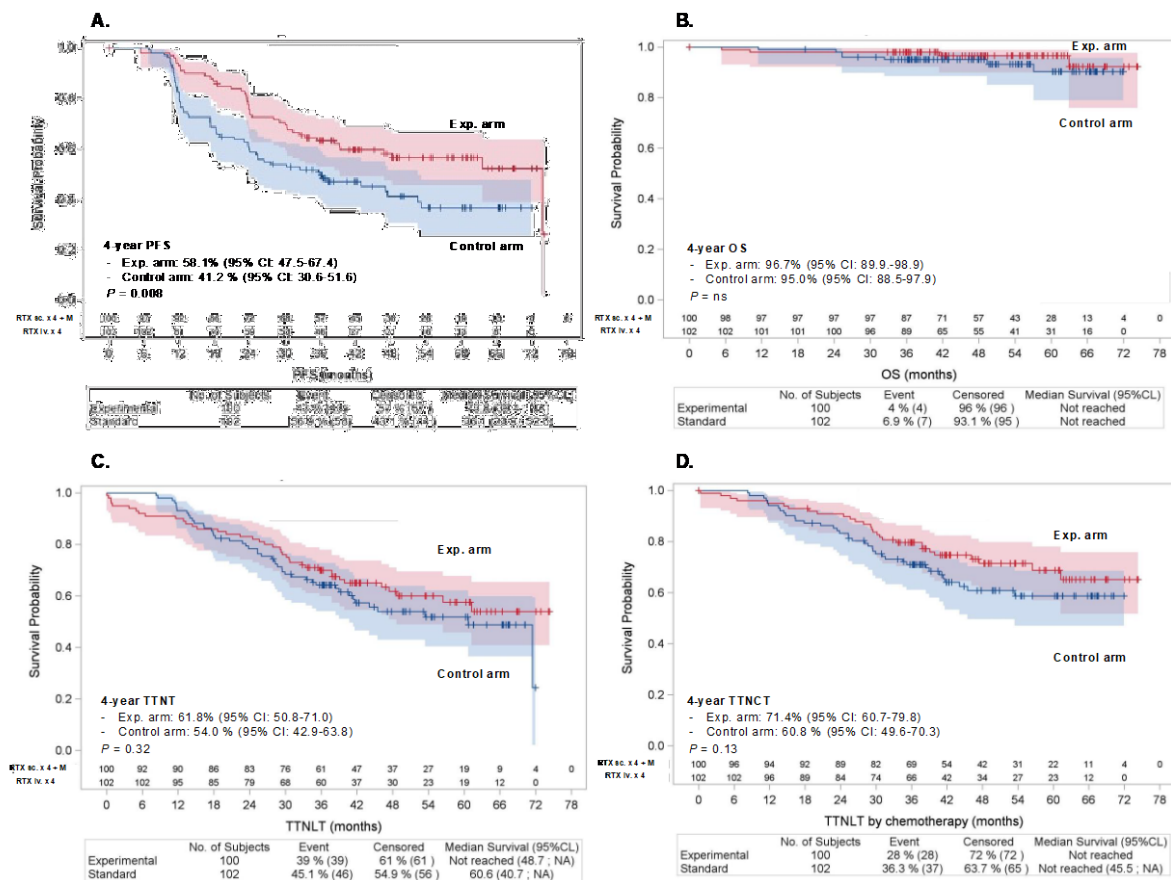


Figure 3. Landmark Survival by Rituximab AUC_{0-M3} and Factors Affecting AUC_{0-M3}

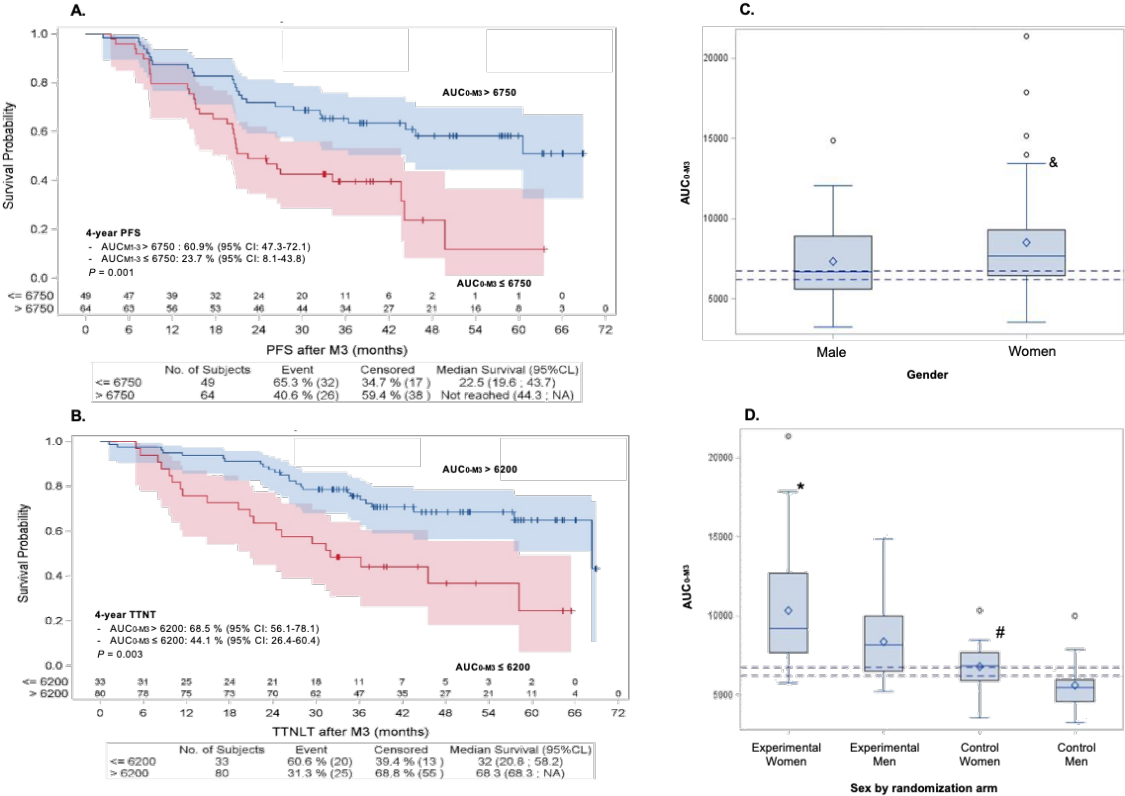


Figure 4. Response at M12 According to Lugano Classification

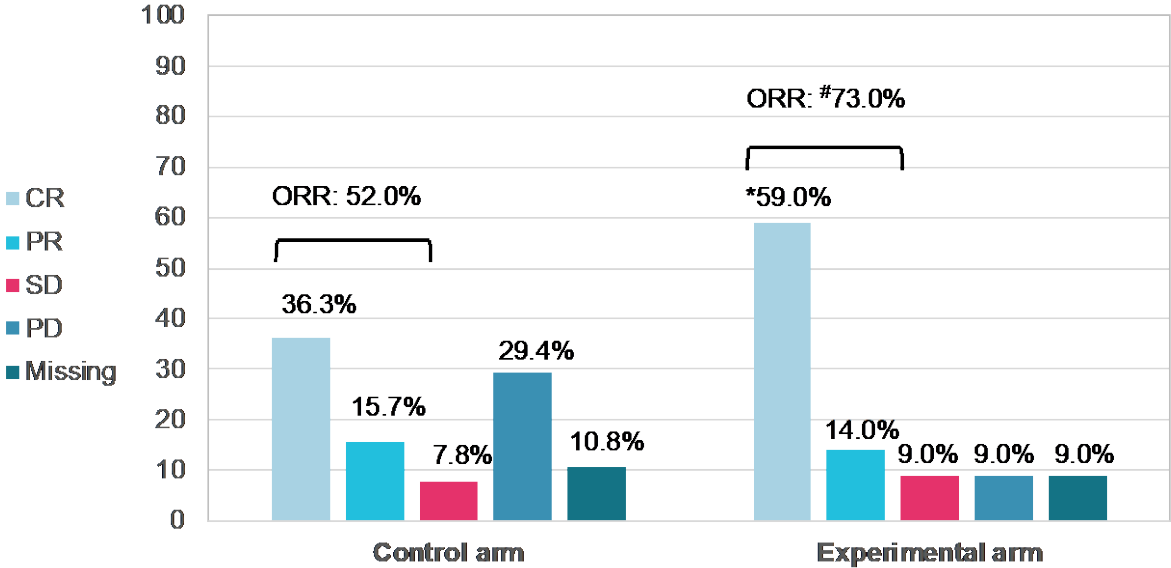
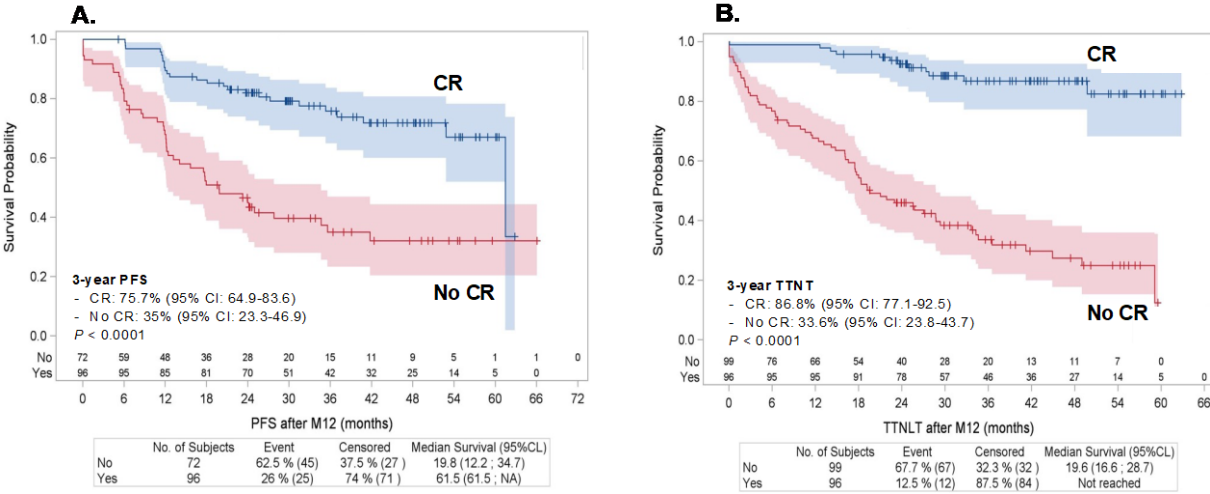
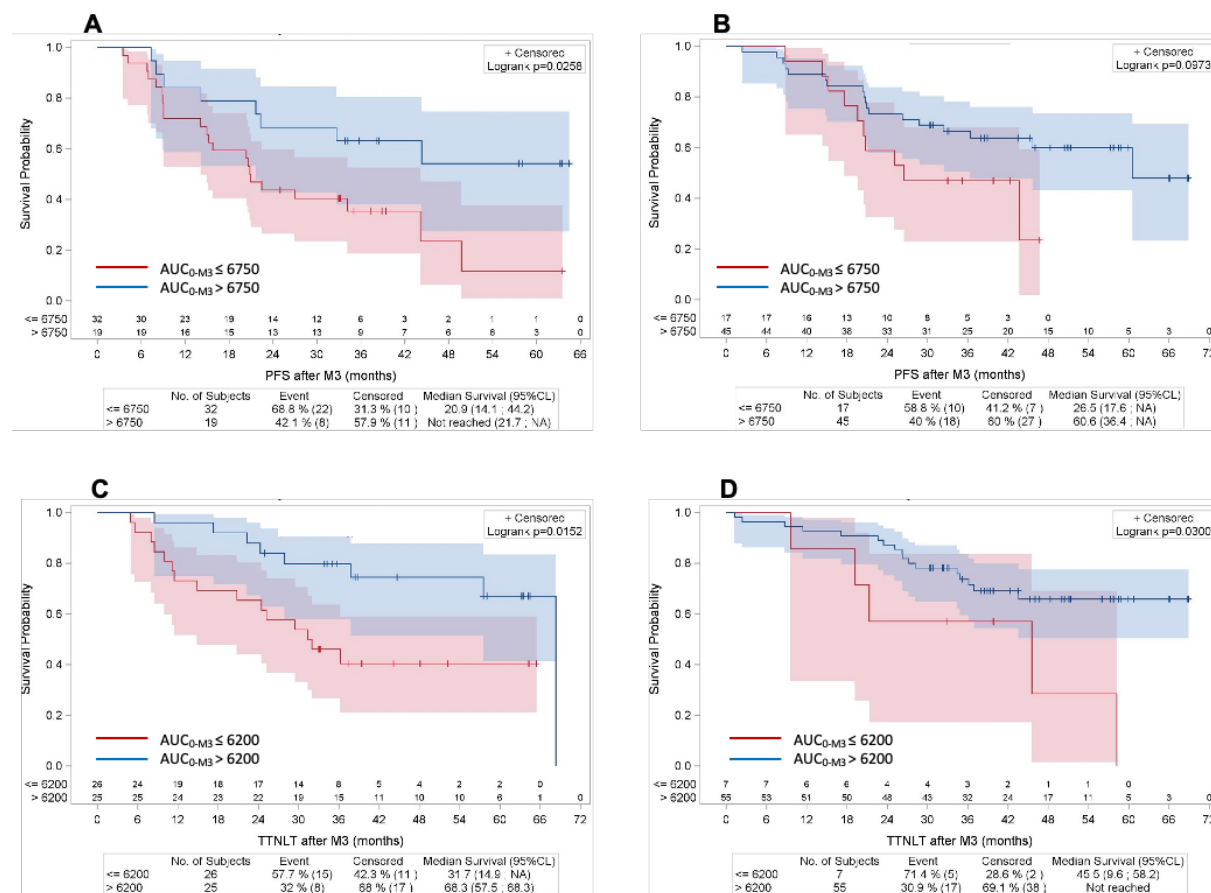


Figure 5. Landmark Survival by Response Status at M12



Supplemental Figure. Landmark Survival by treatment arm according to AUC_{0-M3}.



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

Supplemental methods

Pharmacokinetic data analysis was made using compartmental models and nonlinear mixed-effects modeling (population approach) using Monolix Suite 2020 (Lixoft®, Antony, France). The final model was used to compute values of area under the concentration curve (AUC) for each patient.

Structural model

Our model was based on a two-compartment model with first-order absorption, distribution, and elimination rates. As in previous studies, the effect of antigen mass on rituximab pharmacokinetics [1, 2] was implemented as a time-varying clearance component as in previous studies [3-5], which led to a better description of concentration-time data than target-mediated drug disposition (TMDD) model with irreversible binding approximation.[6-9] The model was implemented as follows:

$$\frac{dC_C}{dt} = In(t) - \frac{CL_0 + CL_1 \cdot \exp(-k_{des} \cdot t)}{V_1} \cdot C_C - \frac{Q}{V_1} \cdot C_C + \frac{Q}{V_2} \cdot C_P$$

$$\frac{dC_P}{dt} = \frac{Q}{V_1} \cdot C_C - \frac{Q}{V_2} \cdot C_P$$

Where C_C and C_P are rituximab concentrations in central and peripheral compartments, respectively, $In(t)$ is rituximab input function, V_1 and V_2 are central and peripheral volumes of distribution, respectively, CL_0 and Q are target-free systemic and intercompartment clearances, respectively, CL_1 is time-varying component of systemic clearance and k_{des} is first-order decline of CL_1 . In addition, since rituximab was administered either by IV or subcutaneous (SC) route, SC bioavailability was estimated. Rituximab absorption kinetics following SC injection was described using a first-order absorption rate constant (k_a) as for most of SC monoclonal antibodies.[1]

Statistical models

Interindividual model. Pharmacokinetic parameters were assumed to follow a lognormal law, interindividual model was therefore exponential i.e. $\theta_i = \theta_{TV} \cdot \exp(\eta_i)$, where θ_i is the estimated individual parameter, θ_{TV} is the typical value of the parameter and η_i is the random effect for the i^{th} patient. Values of η_i were assumed to be normally distributed with mean 0 and variance ω^2 . The parameter F was assumed to follow a probit law since varies strictly between 0 and 1. Interindividual variances that could not be estimated properly were fixed to 0. In the present study, interindividual variances of V_1 , CL_0 , CL_1 , V_2 and F . Interindividual variances of k_a , k_{des} and Q were not estimable and were therefore fixed to 0.

Residual model. Additive, proportional and mixed additive-proportional models were tested.

Model comparison and selection

Several structural models were tested, one-compartment and two compartment models with first-order distribution and elimination rate constants, then irreversible binding target-mediated elimination as in our previous works [6-9] and time-varying clearance as in previous other works. [3-5] Structural models were compared using Akaike's information criterion (AIC), defined as $AIC = OFV + 2.p$, where OFV is the value of the objective function and p is the number of model parameters to estimate. Interindividual and residual models were chosen by comparing nested models on the basis of the OFV tested using a likelihood ratio test (LRT). The two-compartment model with time-varying clearance led to a better description of concentration-time data (AIC=10504.28) compared to irreversible binding target-mediated elimination (AIC=10556.00), two-compartment model with first-order elimination rate (AIC=10572.70) or one-compartment model with first-order elimination rate (AIC=11519.22).

Model goodness of fit and evaluation

The goodness-of-fit was assessed for each model by plotting population-predicted (PRED) and individually predicted (IPRED) concentrations versus observed concentrations (DV) and IPRED and DV versus time. Population predictions were obtained using typical parameters, which include explained variability (i.e. population estimates and covariates), whereas individually predicted concentrations were obtained using individual parameters, which include both explained and unexplained (i.e. the random effects η_i for each PK parameter). In addition, the goodness-of-fit was evaluated by the distribution of residuals evaluated by graphical inspection of population (PWRES) and individual (IWRES) weighted residual distributions, visual predictive checks (VPC), and normalized prediction distribution errors (NPDE). These residuals should follow a standard normal distribution (i) to confirm a satisfactory description of the data using the model and (ii) to allow LRT tests (figure 1.)

Covariate analysis

Continuous covariates that were tested were baseline levels of alanine (ALAT) and asparagine (ASAT) aminotransferases, bilirubin (BILI), creatinine (CREAT), gamma-glutamyl transferase (GGT), immunoglobulins (IGG), lactate dehydrogenase (LDH), white blood cell (WBC) and lymphocyte (LYM) counts, number of nodal sites, (NNS), number of nodal areas (NNA), median of maximal standardized uptake value obtained by PET-CT (SUV), body weight (BW), body surface area (BSA) and height (HT). All of these covariates, except for NNS and NNA were coded as a power function and centered to their median. Categorical covariate was sex, with females taken as a reference. The influence of each covariate on statistical models was based on the During univariable step, the association of each covariate was tested. Each covariate showing a significant influence ($\alpha < 0.1$) was kept for multivariable step. During the multivariable step, a forward and backward stepwise selection process was performed, where covariates were added and then removed during forward and backward steps, respectively. Covariates which inclusion ($\alpha < 0.05$) in forward or which exclusion ($\alpha < 0.01$) during backward steps were retained in the final model.

The final covariate model presented (table 1) increased V_1 with BSA ($p=4.19.10^{-6}$) and HT ($p=0.00041$), increased or decreased CL_1 with BSA ($p < 10^{-16}$), and NNA ($p=0.0027$), or CREAT ($p=0.01$), respectively, increased CL_1 with NNA ($p=0.0055$) and increased V_2 with BSA ($p=7.2.10^{-7}$).

The final statistical model was therefore:

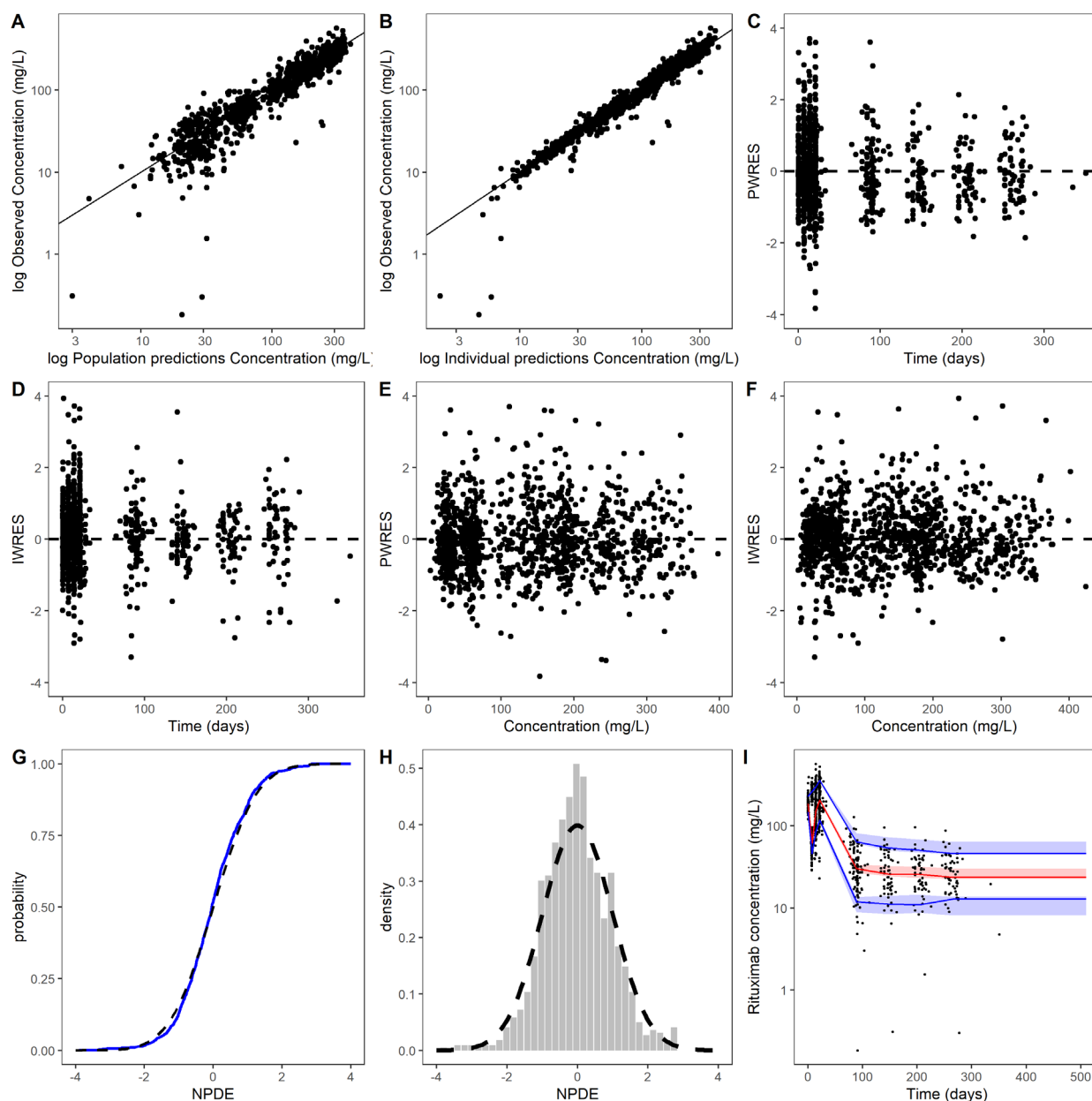
$$F = 0.76 \cdot e^{\eta_{F,i}}$$

$$V_1 = 3.5 \cdot \left(\frac{BSA}{1.87}\right)^{0.74} \cdot \left(\frac{HT}{169}\right)^{1.4} \cdot e^{\eta_{V_1,i}}$$

$$CL_0 = 0.21 \cdot \left(\frac{BSA}{1.87}\right)^{2.0} \cdot \left(\frac{CREAT}{70}\right)^{-0.27} \cdot e^{0.027 \cdot NNA} \cdot e^{\eta_{CL_0,i}}$$

$$CL_1 = e^{0.090 \cdot NNA} \cdot e^{\eta_{CL_1,i}}$$

$$V_2 = 3.5 \cdot \left(\frac{BSA}{1.87}\right)^{1.6} \cdot e^{\eta_{V_2,i}}$$



Supplemental Figure 1. Goodness-of-fit charts of the PK model. Legends: (A) Observed rituximab concentration vs population prediction (PRED); and (B) observed rituximab concentration vs individual prediction (IPRED). Solid black line represents the identity line. (C) Population (PWRES); and (D) Individual-weighted residuals (IWRES) vs time; and (E) Population; and (F) Individual-weighted residuals (IWRES) vs individual prediction; (G) Normalized prediction distribution error (NPDE) distribution vs. Gaussian density; and (H) probability. Dashed line is theoretical Gaussian distribution; (I) Visual predictive check (VPC) plot. Observed (black circles) concentrations, empirical (continuous lines) percentiles (from bottom to top: 10%, 50% and 90% percentiles) and prediction interval (from bottom to top: 10%, 50% and 90% prediction intervals).

Supplemental Table 1. Pharmacokinetic parameter estimates for base and final models.

Parameter	Unit	Model			
		Base model		Final model	
		Estimate	RSE%	Estimate	RSE%
k_a	day ⁻¹	0.21	6.3	0.22	12
F	—	0.80	3.1	0.76	3.7
V_1	L	3.5	2.1	3.5	2.4
CL_0	L.day ⁻¹	0.25	3.5	0.21	5.2
CL_1	day ⁻¹	0.068	30	0.10	28.0
k_{des}	day ⁻¹	0.029	20	0.056	13.0
V_2	L	3.9	4.6	3.5	6.4
Q	L.day ⁻¹	0.76	2.1	0.69	18.0
BSA_ V_1	—	—	—	0.74	22
HT_ V_1	—	—	—	1.4	29
BSA_ CL_0	—	—	—	2.0	9.5
NNA_ CL_0	—	—	—	0.027	33
CREAT_ CL_0	—	—	—	-0.27	39
NNA_ CL_1	—	—	—	0.090	36
BSA_ V_2	—	—	—	1.6	16
ω_F	—	0.44	17	0.41	14
ω_{V1}	—	0.17	10	0.097	18
ω_{CL0}	—	0.29	8.0	0.21	7.9
ω_{CL1}	—	0.93	19	0.53	15.0
ω_{V2}	—	0.25	12	0.11	46
σ_{add}	mg/L	2.2	18	2.2	18
σ_{prop}	—	0.16	2.9	0.16	2.9

Legends. RSE: relative standard error, k_a : first-order absorption rate constant, F: bioavailability, V_1 and V_2 : central and peripheral volumes of distribution, respectively, CL_0 and Q: target-free systemic and intercompartment clearances, respectively, CL_1 : time-varying component of systemic clearance, k_{des} is first-order decline of CL_1 , ω : interindividual standard deviation, σ : residual standard deviation.

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