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Efficacy and Safety of Frontline Single-Agent Rituximab in Extranodal Marginal Zone Lymphoma

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ABSTRACT

First-line therapy for patients with extranodal marginal zone lymphoma (EMZL) is not well established, except for eradication therapy for *Helicobacter pylori* in early gastric MZL. Various regimens, for example, locoregional treatment and systemic chemo-immunotherapy, can be used depending on the site and stage of disease. Single-agent rituximab is a useful approach in the setting of localized, low-intermediate risk EMZL. The aim our research was to analyze the effectiveness and safety of single-agent rituximab (375 mg/m^2 once weekly for 4 weeks) in naïve EMZL in a real-life setting. The primary endpoint was the overall response rate (ORR), secondary endpoints were progression-free (PFS), overall (OS) and disease-free survivals (DFS), and drug tolerability. Fifty-nine patients were analyzed. Median time between diagnosis and rituximab was 3.6 months. The ORR was 89.9%, with 67.8% complete response (CR). Median DFS and PFS were reached at 6.3 and 5.3 years, respectively. After a median follow-up of 5 years, median OS was not reached. The most common adverse event was infusion reaction, reported in 28 cases, mainly during the first infusion and easily manageable. Single-agent rituximab may represent a valid therapeutic option in the first-line treatment of EMZL, at least for localized disease, with a favorable toxicity profile.

1 | Introduction

Extranodal marginal zone B-cell lymphoma (EMZL), also known as mucosa-associated lymphoid tissue (MALT) lymphoma, is the third most common type of B-cell non-Hodgkin lymphoma (NHL), accounting for approximately 7% of cases [1–3].

This peculiar type of indolent lymphoma can affect virtually any organ site and arises from MALT tissue, either physiologically or pathologically induced by chronic immunological stimulation, such as infections (e.g., *Helicobacter pylori* [HP], *Borrelia burgdorferi*, and *Chlamydia psittaci* in the stomach, skin, and ocular adnexa, respectively) or autoimmune diseases (e.g., Sjögren's syndrome in the salivary glands and Hashimoto's thyroiditis in the thyroid) [2, 4–6].

In the absence of specific guidelines for the management of EMZL, several factors, including the anatomical site involved and its peculiarities, and the indolent nature of the disease, should be considered when planning treatment to maximize efficacy and reduce immediate and long-term toxicities [7]. Apart from HP eradication as the initial treatment for limited gastric EMZL [8–10], there is no consensus on the optimal therapy for patients who fail antibiotics or those with advanced disease or extra-gastric localization.

Camilla Mazzoni and Lisa Argnani equally contributed to the work.

Locoregional treatments, such as surgery and radiotherapy, are often considered the mainstay of initial treatment for localized EMZL [11–15]. When these approaches are not feasible, single-agent rituximab is the treatment of choice. Instead, chemo-immunotherapy is usually considered in advanced, symptomatic, or higher-risk patients with MZL, or after progression on single-agent rituximab or local therapy. There is limited use of systemic treatments in MALT lymphoma, with most available data extrapolated from retrospective reviews or phase II trials with short follow-ups, involving patients with indolent B-cell lymphomas [9, 16].

Rituximab, either alone or combined with chemotherapy, such as chlorambucil or bendamustine, has shown activity in phase II trials in the first-line setting [17–21]. The addition of chemotherapy to the rituximab backbone improves the depth of response and leads to better long-term disease control. However, the IELSG-19 trial reported no difference in overall survival curves between rituximab alone and the rituximab–chlorambucil combination. Nevertheless, the literature on the first-line use of rituximab in EMZL is limited [17–19, 22–24].

We report our single-center experience with frontline single-agent rituximab in EMZL treated outside clinical trials.

2 | Patients and Methods

2.1 | Study Design and Patients

We conducted a single-center, observational, retrospective study. All patients included in the study were 18 years-old or older at enrolment and had a histologically confirmed diagnosis of EMZL not previously treated with any lymphoma therapy other than HP eradication.

We collected all adult patients with a consecutive diagnosis of EMZL from the RETROLYMPH study. This study adhered to the standards of the Helsinki Declaration. All patients were enrolled consecutively after providing written informed consent or authorization from the privacy guarantor for patients who were lost to follow-up or died. The study was approved by our institutional board (Ethical Committee AVEC of Bologna, approval ID 1043/2021/Oss/AOUBo). The study has no commercial support.

2.2 | Treatment and Assessments

Rituximab was administered intravenously at the dose of 375 mg/m^2 once weekly for 4 weeks; if an adverse reaction (AE) prevented completion of the weekly infusion, it was delayed 1 week later with the addition of an appropriate steroid premedication. Indication for treatment were first to resolve the symptoms associated with the disease, and second to obtain a remission lasting over time.

Initial staging included whole-body computed tomography (CT) scan and bone marrow biopsy. Bone marrow biopsy was omitted in patients with an excessive risk of bleeding. Positron emission tomography (PET), magnetic resonance imaging (MRI), and ultrasound of the affected organ were also used for staging in some patients, depending on the location of the disease and clinical features. All positive findings were repeated at the end of induction therapy. End-of-treatment assessments were performed 1–3 months after the last rituximab infusion. The Lugano criteria were used to assess the response to treatment; for patients diagnosed before 2014, the responses have been revised according to the most recent revision [25]. For gastric EMZL, oesophagogastroduodenoscopy (EGD) with multiple biopsies taken from each region of the stomach, duodenum, and gastroesophageal junction was the initial staging method, while echo-endoscopy was used to assess wall infiltration. For response assessment, endoscopy was performed at least 3 months after the last rituximab dose, and all patients underwent random biopsy. All samples were analyzed by pathologists specialized in hematologic diseases.

Safety was assessed by recording all AEs, including their type, incidence, and severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

2.3 | Endpoints

The primary endpoint was to evaluate the best overall response rate (ORR, defined as the sum of complete response rate [CR] and partial response rate [PR]), of single-agent rituximab in the first-line treatment of EMZL.

Secondary endpoints were progression-free survival (PFS), overall survival (OS), disease-free survival (DFS), and time to next treatment (TTNT), all defined according to Cheson et al. [26]. Safety endpoints included incidence of deaths, AEs, serious AEs, AEs leading to discontinuation or dose delay, and specific laboratory abnormalities.

2.4 | Statistical Analysis

PFS was measured from treatment initiation until lymphoma progression or death. OS was measured from treatment initiation until death from any cause. DFS was measured for patients who achieved CR from first response documentation until disease recurrence or death due to lymphoma or acute toxicity from study drug. TTNT was measured from the end of the first treatment until the start of the next treatment; for patients who did not receive a second treatment, it was calculated from the end of treatment until the date of last follow up [26].

Descriptive statistics were used to present patient demographic characteristics and safety data. Survival endpoints were estimated using the Kaplan–Meier method. Statistical analyses were performed with Stata 17 (StataCorp LP, TX).

3 | Results

3.1 | Patient Characteristics

From 2002 to 2019, frontline rituximab was administered to 59 patients diagnosed with EMZL. Most patients had localized, low/intermediate-risk disease (stage IE 83%, IIE

6.8%), with no bone marrow or nodal involvement; B symptoms (3.4%) and blood count abnormalities (22%) were exceptional. Patient characteristics at rituximab start are listed in Table 1.

TABLE 1 | Patient characteristics at rituximab start.

Characteristics	Study population (*n* 59)
Sex, *n* (%)	
Male	29 (49.2)
Female	30 (50.8)
Median age at diagnosis (range)	62.1 (19.4–87.8)
Primary diseases site, *n* (%)	
Orbit, lacrimal glands	11 (18.6)
Skin	6 (10.2)
Parotid	7 (11.9)
Lung	4 (6.8)
Stomach	26 (44)
Other	5 (8.5)
Nodal involvement, *n* (%)	
Present	4 (6.8)
Locoregional	2 (3.4)
Distant	2 (3.4)
Absent	55 (93.2)
Bm involvement, *n* (%)	
Absent	50 (84.7)
Non-diagnostic biopsy	1 (1.7)
Biopsy not done	6 (10.2)
Minimal, not confirmed[a]	55 (93.2)
Splenomegaly	
Absent	57 (96.6)
Present	2 (3.4)
B symptoms, *n* (%)	
Weight loss	2 (3.4)
Absent	57 (96.6)
Abnormal blood count at diagnosis, *n* (%)	
Mild anemia	8 (13.6)
Moderate anemia	1 (1.7)
Thrombocytopenia	4 (6.8)
Thrombocytosis	1 (1.7)
None	46 (78)
M protein, *n* (%)	
Absent	49 (83)
Present	10 (17)
LDH elevated, *n* (%)	
Absent	57 (96.6)
Present	2 (3.4)
Concomitant autoimmune disease, *n* (%)	
Rheumatoid arthritis	3 (5.1)
Immune thrombocytopenia	2 (3.4)
Sjögren syndrome	2 (3.4)
Suspected mixed connective tissue disease	1 (1.7)
Hashimoto's thyroiditis	4 (6.8)
None	48 (81.3)
Hp at diagnosis, *n* (%)	
Positive	8 (13.6)
Negative	36 (61)
Not done	15 (25.4)
Eradication therapy, *n* (%)	
Done	18 (30.5)
Before diagnosis	10 (16.9)
At the time of diagnosis	8 (13.6)
Not done	41 (69.5)
Ann arbor stage, *n* (%)	
IE	49 (83)
IIE	4 (6.8)
IV	6 (10.2)
Malt-IPI score, *n* (%)	
Low risk	34 (57.6)
Intermediate risk	23 (39)
High risk	2 (3.4)
Revised MALT-IPI score, *n* (%)	
Low risk	20 (33.9)
Intermediate-low risk	35 (59.3)
Intermediate-high risk	3 (5.1)
High risk	1 (1.7)

Abbreviations: BM, bone marrow; HP, *Helicobacter pylori*; IPI, international prognostic index; LDH, lactate dehydrogenase; MALT, mucosa-associated lymphoid tissue.
[a]Small lymphoid infiltrate, suspicious for disease localization but not characterizable by immunohistochemistry.

3.2 | Effectiveness

The median time between diagnosis and rituximab start was 3.6 months (range, 0.8–35.9 months).

Five patients received additional therapies in combination with rituximab: 4 patients underwent diagnostic excisional surgery followed by rituximab as consolidation; in 1 patient with primary cutaneous MZL, rituximab was followed by radiotherapy of the previously involved skin area (total dose 24 Gy, fractionated in 12 sessions). The 4 patients who underwent eradication surgery had negative post-surgery imaging, but histological analysis did not allow assessment of neoplastic infiltration of the margins. The only patient who received subsequent radiotherapy had a complete response after rituximab, and RT was used as consolidation treatment.

The ORR was 89.9%, with 40 patients (67.8%) achieving CR, 13 (22%) PR and six (10.2%) SD (Figure 1). No disease progression was observed at the end of therapy. Five patients in PR at the first assessment at 2.87 months (range, 0.93–3.93) converted in CR at a median of 8 months (range, 5.37–14.73) without further treatment. Effectiveness by primary site of disease is shown in Table 2.

Overall, out of the 40 patients in CR, 12 relapsed and required at least one second-line therapy. Furthermore, 14 out of the 19 patients in PR or SD received salvage treatment. The most frequently used second-line treatment was a combination of rituximab and bendamustine, which resulted in CR for most patients (11 out of 12 treated).

Five patients received rituximab re-treatment: three relapsed after achieving a first CR (duration of response to first-line therapy was 6.28, 3.44, and 1.46 years, respectively), while two patients were in PR after first-line therapy. Time from end of first line to re-treatment was 6.77, 4.48, and 1.88 years for patients in CR, while it was 5.17 and 3.57 months for patients in PR. Three out of five patients who received re-treatment with rituximab achieved CR.

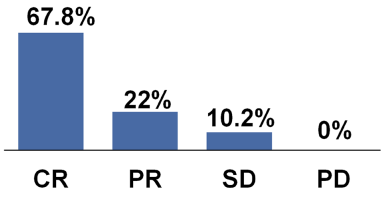

FIGURE 1 | Responses to frontline treatment with rituximab for the overall cohort. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Of the 31 patients who relapsed or were refractory after frontline rituximab, 19 eventually achieved a CR with subsequent lines of therapy; the median number of lines of therapy (excluding eradication and watch and wait regimens) was one (range 1–6); only six patients received three or more lines of therapy. Two patients relapsed shortly before the study data cut-off date, and information on subsequent treatment is not available. No histological transformation was observed.

Median TTNT was reached at 5.4 years; namely 79.1%, 66%, and 52% of patients were treatment-free at 1, 2, and 5 years (Figure 2A). DFS at 1, 2, and 5 years for the 40 patients in CR was 89.9%, 87.3%, and 61.8%, respectively, while the median DFS was reached at 6.3 years (Figure 2B). Median PFS was reached at 5.2 years, whereas PFS at 1, 2, and 5 years was 84.7%, 74.4%, and 58.5%, respectively (Figure 2C). After a median follow-up of 5 years, the median OS was not yet reached at time of analysis. Estimated OS at 1, 2, 5, and 10 years was 100%, > 96%, > 94%, and > 77%, respectively (Figure 2D). A total of six deaths occurred. Of these, five patients were over 90 years of age, two of whom had active disease at the time of death. It is unclear whether lymphoma was the definite cause of decease. One patient died in CR at the age of 78 due to other cause than lymphoma.

3.3 | Safety

All patients receiving at least one rituximab infusion were included in the safety analysis. Twenty-two patients did not experience any AE (37.3%). Hematological toxicity was very rare, with only one patient experiencing combined grade 2 anemia and grade 3 neutropenia.

Infusion reactions were the most frequent non-hematological AEs, reported in 28 cases (47.5%). Of these, 27 occurred during the first infusion, while only one was observed during the third rituximab infusion. Of the 28 reactions observed, 25 were grade 2, while two were grade 1 and one was grade 3. The clinical presentation of infusion reactions varied widely, with the most common symptoms being discomfort and pruritus of the aerodigestive tract, pharyngodynia, cough, urticaria, pruritus, chills, hypertension, nausea, occurring alone or concurrently in the same patient. In most cases, the infusion reactions were effectively managed by reducing or stopping the infusion and administering saline and appropriate drugs: glucocorticoids such as hydrocortisone or methylprednisolone, calcium gluconate, and paracetamol were among the most used. If a severe reaction prevented the continuation of therapy, the infusion was delayed, and the patient was given an adequate steroid premedication before subsequent administrations. The safety profile is summarized in Table 3.

TABLE 2 | Response according to most frequent EMZL site.

Site (*n*)	CR, *n* (%)	PR, *n* (%)	SD, *n* (%)	≥ 2 lines of therapy, *n* (%)
Stomach (26)	17 (65.4)	7 (26.9)	2 (7.7)	13 (50)
Ocular adnexa (11)	5 (45.4)	3 (27.3)	3 (27.3)	8 (72.7)
Parotid (7)	7 (100)	0 (0)	0 (0)	1 (14.3)
Cutaneous (6)	4 (66.7)	2 (33.3)	0 (0)	4 (66.7)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

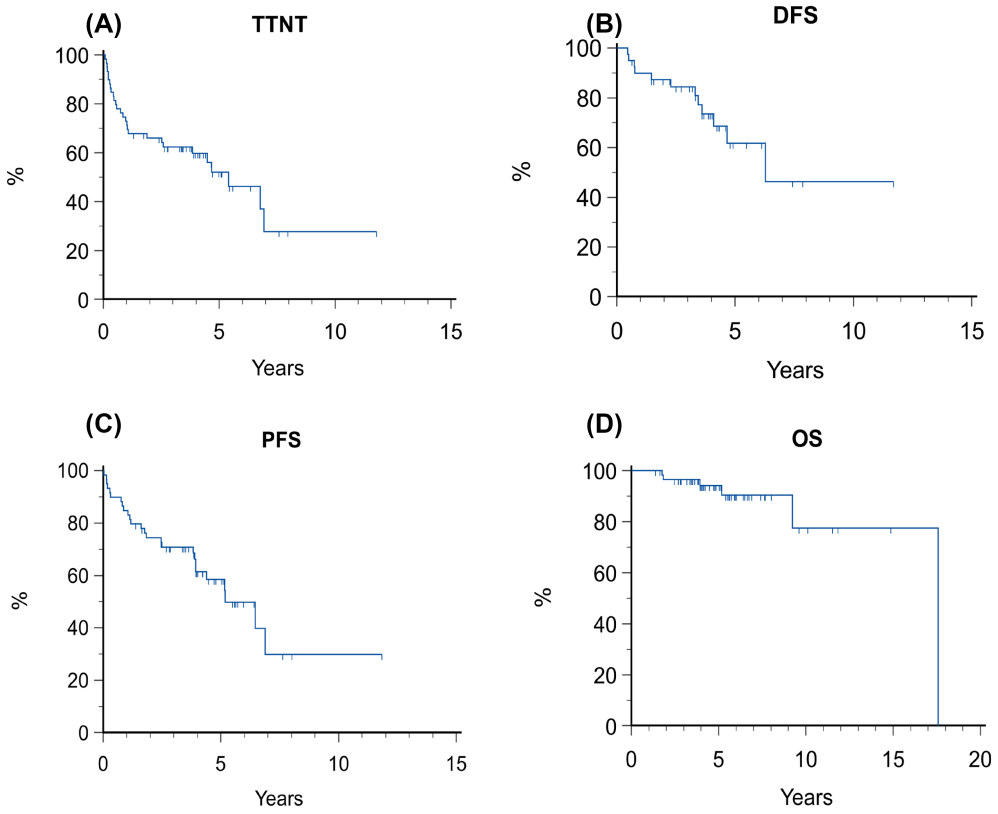

FIGURE 2 | (A) time to next treatment (TTNT); (B) disease-free survival (DFS); (C) progression free survival (DFS); and (D) overall survival (OS) for the entire study population.

TABLE 3 | Toxicity.

Adverse events	Total, *n*	Grade ≥ 3, *n*
Hematological toxicity		
Anemia	1	—
Neutropenia	1	1
Non hematological toxicity		
Infusion reactions	28	1
Asthenia	6	—
Fever	5	—
Skin rash	3	—
Abdominal pain	2	—
Hypertension	1	1
Other	8	—

Overall, only one patient discontinued rituximab due to the grade 3 infusion reaction mentioned above; this reaction occurred during the first dose administration and led to definitive treatment discontinuation. The patient received second line bendamustine monotherapy for six cycles.

4 | Discussion

The literature on rituximab treatment in the first line setting for EMZL is sparse, and published studies often present small sample sizes, heterogeneous endpoints, and a diversity of patients in characteristics and previous lines of therapy. Importantly, most study populations included other types of MZL or even cases of other indolent lymphomas (Table 4) [17–19, 22–24]. The objective of the present research study was to evaluate the effectiveness in terms of ORR and survivals and safety of rituximab in the frontline setting of MALT lymphoma, in routine clinical practice.

Rituximab is generally preferred to radiotherapy in the management of some limited-stage EMZL located in non-irradiated areas or whose radiotherapy exposure may cause serious adverse effects. Radiotherapy is indeed efficacious: CR rates ranges between 90% and 100%, median PFS around 15 years and 10-year DSF and 5-year OS of 80% and 90%, respectively, but toxicity, in particular late-onset severe post actinic disease, remains a major concern and affects 1%–5% of the patients. The majority of these studies used a dose > of 30 Gy, while more recent evidence suggests that a lower dosage of 24 Gy is equally effective and less toxic, and thus represents the standard recommended dose [11–15].

To our knowledge, this monocentric study of 59 patients is one of the largest real-life experiences ever published for EMZL. Our study sample was representative of the overall patient population in terms of age, sex, symptoms, and disease sites. However, advanced stage with nodal or bone marrow involvement and unfavorable risk disease were under-represented, as most of our patients had localized, low or intermediate risk EMZL according to MALT-IPI or revised MALT-IPI scores [27, 28]. First, this is due to selection bias, as rituximab

TABLE 4 | Published experiences with single-agent rituximab in naïve EMZL patients.

Study	EMZL, *n*	Rituximab schedule	ORR, %	CR, %	Other endpoints assessed	Notes
Conconi et al. [17]	35 (35 [23[a]])	375 mg/m^2 × 4 weeks	87	47.8	Median TTF of 22 months	
Raderer et al. [22]	9 (9 [8[a]])	375 mg/m^2 × 4 weeks	55.5	55.5		The response was evaluated for all the 9 patients with EMZL
Martinelli et al. [23]	26 (26 [15[a]])	375 mg/m^2 × 4 weeks	76.9	46.2	DFS at 28 months 54% OS at 28 months 100%	The response was evaluated for the 26 patients with EMZL who completed scheduled treatment course
Lossos et al. [18]	16 (12 [10[a]])	375 mg/m^2 × 4 weeks	62.5	18.8	Median TTF 4 months (range, 6–53)	The response was evaluated for all the 16 patients with EMZL
Williams et al. [24]	71 (38 [38[a]])	375 mg/m^2 × 4 weeks	39.5	15.8		The study compares maintenance treatment with rituximab to repeat treatment. The data are extrapolated from the induction phase of the study
Zucca et al. [19]	138 (138 [138[a]])	375 mg/m^2 × 8 weeks	78.3	55.8	Median EFS 5.6 years DFS at 5 years 66% Median PFS 6.9 years OS at 5 years 92%	Phase III, 3-arm study evaluating the efficacy of the rituximab-chlorambucil combination versus rituximab or chlorambucil monotherapy. The survival endpoints refer to the 138 patient in the single-agent rituximab arm

Abbreviations: CR, complete response; DFS, disease-free survival; EMZL, extranodal marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.
[a]Treatment-naïve patients.

monotherapy is preferred for limited-stage disease with a favorable prognosis, whereas the treatment of advanced, high-risk EMZL often involves combined chemo-immunotherapy. Second, in our center, rituximab is generally preferred to radiotherapy in the management of localized EMZL, especially in sites that are difficult to irradiate or in large areas that require a wide field of radiation, because it is usually well tolerated and has fewer long-term AEs. Finally, some advanced-stage diseases may have been missed due to the lack of standardization of staging methods. Also, the prevalence of HP infection in our study was lower than that reported in the literature in patients with gastric EMZL (23.1%): this may be explained by the decreasing rate of infection reported by other authors as well as the use of prior eradication therapy in nine of the 20 HP negative cases of gastric EMZL [29–32].

Two phase 2 trials used the standard rituximab monotherapy schedule (375 mg/m^2 every week, for four consecutive weeks) in gastric and extra gastric EMZL, regardless of stage, and included both untreated patients and, unlike our study, patients who had failed a previous line of treatment (antibiotics, chemotherapy or radiotherapy). As a result, ORR and CR rates are lower compared to our study, 67% and 73% versus 89.9% and 17% and 44% versus 67.8%, respectively [17, 18]. In addition, Conconi et al. [17] reported a trend towards better outcomes in treatment-naive patients, with a median TTF of 22 months compared to 12 months in previously exposed patients ($p = 0.001$).

The IELSG-19 trial is an international, prospective, open-label, phase III, 3-arm study evaluating the efficacy of the rituximab–chlorambucil combination versus rituximab or chlorambucil monotherapy in patients with previously untreated MALT lymphoma. Despite differences in study design and primary endpoint, the single-agent rituximab arm of this trial is the best available comparison with our data. However, it is important to note that in the IELSG-19 study, rituximab was administered weekly for 4 weeks and then every 28 days thereafter for up to eight doses [19].

Again, the ORR and CR rates were lower than those described in the present study (ORR 78.3% vs. 55.8%, CR 55.8% vs. 67.8%). The trend towards a slightly lower response rate in IELSG-19 may be due to the difference in the two study samples: patients recruited in IELSG-19 generally had more advanced disease (stage III-IV 45.6% vs. 10.2% in our study), a higher frequency of nodal (25.4% vs. 6.8%) and bone marrow involvement, a higher frequency of elevated LDH levels and involvement of two or more sites, and eight out of 138 patients had already received locoregional therapy [19]. Regarding the long-term endpoints, there are no significant differences in OS, while PFS and DFS are longer in IELSG-19 than in the present study: these could be explained by the diverse number of rituximab doses (eight in IELSG-19, four in our study), as already showed by Williams et al. [24] On the other hand, the number of doses does not seem to influence the depth of response to induction therapy. Therefore, it is desirable to design new studies to evaluate the optimal number of rituximab doses during the induction phase. This will help to determine the best schedule in terms of response duration and toxicity. Currently, there is a lack of such studies in the literature.

The incidence and severity of AEs in both hematological and non-hematological toxicity were similar between IELSG-19 and our study [19]. However, we observed a higher frequency of infusion reactions in our study (28 vs. 20), despite the much smaller sample size. In addition, some grade 3–4 adverse events (infection, fever, pancreatitis, and elevated transaminases) were observed in a small number of patients in the IELSG-19 study and are probably due to the larger study sample, which would include patients with rare and specific sensitivities to rituximab not included in our study.

Finally, in our study, some of the PR seen at the first re-evaluation gradually converted to CR without further treatment, like responses after HP eradication therapy. This could be explained by the longer time required for rituximab to activate the immune response. Although no study in the literature has directly highlighted this phenomenon, available data suggests that the optimal response was achieved 6–7 months after the start of therapy [17, 19, 22]. Therefore, if the patient does not achieve a CR at the first re-evaluation and there is no clinical need to start a new line of therapy immediately, it may be reasonable to wait and re-evaluate the response at later intervals.

This study has three main limitations: the retrospective, monocentric design, the small sample size (albeit in the context of a rare disease). These aspects do not allow definitive conclusions to be drawn, particularly regarding long-term efficacy, nevertheless represent one of the most extensive experiences currently available in the literature.

In conclusion, our study has shown that single-agent rituximab may be a valid therapeutic option in the first-line treatment of MALT lymphoma, at least for localized, low/intermediate risk disease. Its choice over alternative treatments, such as radiotherapy and chemotherapy, is justified by the indolent nature of MALT lymphoma, with treatment aimed at maintaining a reasonable quality of life rather than improving OS, given the availability of effective salvage treatments for relapse. Therefore, careful assessment of the relationship between treatment efficacy and toxicity is crucial in the choice of therapy.

Author Contributions

Camilla Mazzoni: conceptualization, data curation, investigation, methodology, validation, writing – original draft, writing – review and editing. **Lisa Argnani:** conceptualization, data curation, formal analysis, methodology, validation, writing – original draft, writing – review and editing. **Beatrice Casadei:** data curation, investigation, validation, writing – review and editing. **Alessandro Broccoli:** data curation, investigation, validation, writing – review and editing. **Giulia Gabrielli:** data curation, investigation, validation, writing – review and editing. **Nicole Fabbri:** data curation, investigation, validation, writing – review and editing. **Gabriele Gugliotta:** data curation, investigation, validation, writing – review and editing. **Cinzia Pellegrini:** data curation, investigation, validation, writing – review and editing. **Matteo Carella:** data curation, investigation, validation, writing – review and editing. **Gianmarco Bagnato:** data curation, investigation, validation, writing – review and editing. **Marianna Gentilini:** data curation, investigation, validation, writing – review and editing. **Alice Morigi:** data curation, investigation,

validation, writing – review and editing. **Pierluca Maglio:** data curation, investigation, validation, writing – review and editing. **Martina Cantelli:** data curation, investigation, validation, writing – review and editing. **Vittorio Stefoni:** data curation, investigation, validation, writing – review and editing. **Pier Luigi Zinzani:** conceptualization, funding acquisition, methodology, project administration, supervision, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

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