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# 1 **Immunochemotherapy versus rituximab in anti-MAG** 2 **neuropathy: a report of 64 patients**

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24

25 **ABSTRACT**

26 Monoclonal immunoglobulin M (IgM) anti-myelin-associated glycoprotein (MAG)  
27 neuropathy is a rare disabling condition, most commonly treated with rituximab monotherapy  
28 (R), which leads to neurological improvement in only 30%-50% of patients. The combination  
29 of rituximab plus chemotherapy has been proven to improve the level of responses. We  
30 studied the outcomes of anti-MAG neuropathy patients treated either by R, or by  
31 immunochemotherapy (ICT) in our centre, focusing on the incidence of the first neurological  
32 response evaluated by the modified Rankin Scale (mRS). From 2011 to 2018, 64 patients  
33 were studied: 34 were treated with R and 30 with ICT. According to our treatment decision-  
34 making process, the median mRS was higher in the ICT group (mRS 2) compared to the R  
35 group (mRS 1). At 1 year, mRS improvement rates were 46% and 18% of the ICT and R  
36 groups of patients respectively, with a median time to response of 8 and 13 months ( $p=0.023$ ).  
37 Adverse effects were higher in the ICT group: 62% vs 15% ( $p<0.01$ ) all grades included. One  
38 secondary acute leukaemia occurred 5 years after treatment by ICT. In conclusion, ICT may  
39 be used as a valid option for patients with rapidly progressive and/or severe anti-MAG  
40 neuropathy symptoms.

41

42

## 43 INTRODUCTION

44 Monoclonal gammopathy of clinical significance (MGCS) is defined by the presence in the  
45 serum of monoclonal immunoglobulin (Ig) or monoclonal free light chain produced by  
46 indolent B-cell clones in the absence of overt tumour proliferation but responsible for organ  
47 damage because of toxicity of the monoclonal component.(1) Mechanisms of toxicity include  
48 deposition of all or part of the monoclonal Ig, immune complex formation, complement  
49 activation or autoantibody activity against a tissue antigen. Any antibody activity against  
50 myelin-associated glycoprotein (MAG) may be responsible for IgM anti-MAG antibody-  
51 related peripheral neuropathy which is a rare, disabling condition. Most frequently, there is no  
52 overt lymphoproliferative syndrome but monoclonal gammopathy of undetermined  
53 significance (MGUS) occurs. However, in 33% of cases, Waldenström macroglobulinemia  
54 (WM) or indolent B-cell lymphoma is present.(2) The ensuing neuropathy is characterized by  
55 mostly sensitive disorders and is generally slowly progressive but there is great heterogeneity  
56 of clinical presentation among patients, and progression can lead to irreversible secondary  
57 axonal loss with disabling neurological outcomes. Rarely, acute worsening can occur and lead  
58 to major and rapid disability. (3). It is estimated that 20%-45% of patients are disabled by  
59 severe progressive neuropathies that undermine their quality of life. (2,4) Thus, there is a need  
60 to develop effective treatments. The criteria required to initiate treatment are difficult to  
61 establish in anti-MAG neuropathy because of its rarity, its heterogeneous progressive course,  
62 the subjectivity of symptom presentations and the non-standardized evaluation criteria.(5,6)  
63 Usually, treatment is warranted in case of significant disability and should not be based on  
64 IgM and/or anti-MAG levels. There are no clearly established therapeutic recommendations  
65 and there is insufficient evidence from most pilot studies to recommend any particular  
66 treatment. Rituximab monotherapy use is more and more frequent although its effectiveness  
67 has not been demonstrated by all groups. (5,7–9) Clinical scales improvement with rituximab  
68 monotherapy is reported in 30% to 50% of cases with a median delay of improvement ranging  
69 from 9 to 12 months. (10)

70 In WM and other lymphoproliferative disorders, immunochemotherapy (ICT) yields better  
71 outcomes than rituximab monotherapy (11). In the context of MGCS, the treatment decision is  
72 based on the benefit-to-risk approach and frequently involves chemotherapy.(1) Indeed,  
73 rituximab may be combined with chemotherapy to target the underlying B-cell clone  
74 responsible for the production of anti-MAG antibodies and has been reported by several  
75 teams. (12–15). Our centre has shown that the addition of chemotherapy makes it possible to

76 obtain a faster clinical response, the median time to response being 5 months in the ICT group  
77 compared to 9.5 months in the rituximab group.(16) It is suggested that ICT may be preferred  
78 in case of rapid and/or severe neurological symptoms.

79 Based on these findings, we investigated whether patients with anti-MAG neuropathy would  
80 benefit from more intensive treatments. Here, we report the outcomes of a retrospective **series**  
81 of patients treated with rituximab (R) or rituximab plus chemotherapy at a single centre.

## 82 **MATERIALS AND METHODS**

### 83 **Patients**

84 Recruitment was conducted retrospectively based on medical records. The inclusion criteria  
85 were patients with anti-MAG neuropathy treated with R alone or in combination with  
86 chemotherapy. The diagnosis was related to the association of demyelinating neuropathy  
87 based on EMG features, clinical data matching and monoclonal gammopathy of the IgM type  
88 with anti-MAG activity. Clinical evaluation was assessed with the modified Rankin Scale  
89 (mRS; **Table 1**). IgM levels were assessed with protein electrophoresis and anti-MAG  
90 antibodies with ELISA (Bühlmann, Switzerland) using coated human MAG and peroxidase-  
91 conjugated anti-human IgM. Samples  $\geq 5,000$  BTU were considered as positive. Clinical data  
92 were obtained in accordance with the declaration of Helsinki and with ethical approval from  
93 national (CNIL 2212382) and local (CPP Ile-De-France 05/21/2014) ethics committees. All  
94 patients were informed and oral non opposition of each patient was recorded in medical files  
95 according with the ethical French law. Sixteen patients have been previously described with  
96 shorter follow-up. (16)

### 97 **Treatments**

98 The treatment decision was made according to the patient's symptoms, the impact on daily life  
99 and the natural course of the disease, independently of bone marrow evaluation. ICT was used  
100 to treat the patients with high mRS (3-4) and/ or acute or sub-acute ( $\leq 6$  months) neurological  
101 worsening of the disease, subject to the age and the general status. Patients treated with ICT  
102 received 6 cycles of: dexamethasone (20 mg day 1) plus R ( $375 \text{ mg/m}^2$  day 1) plus oral  
103 cyclophosphamide ( $300 \text{ mg/m}^2$  day 1 to 5) (DRC), or oral fludarabine ( $40 \text{ mg/m}^2$  day 1 to 3)  
104 plus oral cyclophosphamide ( $250 \text{ mg/m}^2$  day 1 to 3) plus R ( $375 \text{ mg/m}^2$  day 1) (FCR), or oral  
105 fludarabine ( $40 \text{ mg/m}^2$  day 1 to 5) plus R ( $375 \text{ mg/m}^2$  day 1) (FR), or bendamustine (90

106 mg/m<sup>2</sup> day 1 and 2) plus R (375 mg/m<sup>2</sup> day1) (BR). In the R group, R was given: 375 mg/m<sup>2</sup>  
107 intravenous every week for 4 weeks.

## 108 **Outcomes**

109 The study's primary endpoint was the incidence of the first mRS improvement. Improvement  
110 was defined as mRS decrease  $\geq 1$ , stabilization as stable mRS, and progression as mRS  
111 increase  $\geq 1$ . The secondary endpoint was the survival without initiation of a new treatment  
112 defined as the time from the start of treatment and initiation of a new treatment or death. We  
113 also evaluated the electrophysiological change (improvement, stability, worsening), according  
114 to Lunn and Nobile-Orazio, (17) the anti-MAG change (decrease defined as  $\geq 25\%$  titre  
115 decrease, increase defined as  $\geq 25\%$  titre increase, stability otherwise) and the IgM change  
116 (decrease defined as  $\geq 25\%$  level decrease, increase defined as  $\geq 25\%$  level increase, stability  
117 otherwise).

## 118 **Statistical analysis**

119 Characteristics of the study population were described in terms of frequencies for qualitative  
120 variables or medians and associated ranges for quantitative variables. Qualitative variables  
121 were compared using Chi-2 test (or Fisher exact test if appropriate ), quantitative variables  
122 were compared using Student test (or non-parametric Wilcoxon test in case of non-normal  
123 distribution). The cutoff date for the analysis was 20/01/2020. Median follow-up was  
124 estimated using reverse Kaplan-Meier. (18)

125 Time to modified Rankin Score (mRS) improvement was defined as the delay between the  
126 start of treatment and the date of event. Patient alive without improvement of modified  
127 Rankin Score were censored at the date of their last known contact or death. Patient who died  
128 before an improvement of modified Rankin score were censored at the date of death. Survival  
129 analyses were performed using the Kaplan-Meier estimate. Incidence of the event was  
130 estimated using the following transformation  $F(t) = 1 - S(t)$  where  $S(t)$  is the Kaplan-Meier  
131 estimate of survival functions.

132 Hazard ratios and their associated 95% confidence intervals were calculated using the Cox  
133 proportional hazard model. For multivariate analysis, we chose to adjust treatment effect on  
134 main confounding factors based on clinical knowledge: mRS at baseline evaluation and speed  
135 of worsening (fast/progressive) assessed before treatment initiation. The proportional hazards  
136 hypothesis was tested for each factor, with Schoenfeld's residuals test and plotting. All tests

137 were two-sided and used a significance threshold at 5%. Analyses were performed with the R  
138 software, version 3.6.3 ([R Development Core Team, 2011](#)).

## 139 **RESULTS**

### 140 **Patients and treatment**

141 From 2011 to 2018, 78 patients with a positive anti-MAG dosage were treated with R or ICT.  
142 Fourteen patients were excluded because of other concomitant indications of treatment  
143 (cryoglobulinemia, CANOMAD syndrome, active WM: n = 4) or lack of data (n = 10). Thus,  
144 64 patients with anti-MAG neuropathy are reported here. Patient characteristics before  
145 treatment are summarized in **Table 2**. The median age at symptom onset was 63 years [IQR  
146 55–69] and 55% of the patients were male. The median time between onset of neuropathy and  
147 treatment initiation was 4.3 years [IQR, 2-7]. The most common symptoms were: sensory  
148 deficit (83%), paraesthesia and dysesthesia (70%) and ataxia (67%). Distal lower limbs motor  
149 deficit was reported for 25 patients (39%), neurological pain for 33 patients (52%) and tremor  
150 for 11 patients (18%). The most frequent type of onset was chronic (>6 months) (81%) but 2  
151 patients had acute progression ( $\leq 1$  month).. The median mRS was 2 [IQR 1–2] in the overall  
152 population, and twelve patients (40%) of the ICT group had mRS of 3 or 4 versus 2 (6%) of  
153 the R group. The median monoclonal peak (for patients with measurable IgM peak, n = 43)  
154 and MAG antibody level (for n = 33 patients with anti-MAG dosage < 70,000 BTU) were,  
155 respectively, 4 g/L [IQR 3–4] and 32,900 BTU [IQR 23,400–43,000]. Thirty-one patients had  
156 anti-MAG antibody levels >70,000 BTU. The kappa isotype was predominant in 81% of  
157 patients. There was no evidence of an overt haematological malignancy in 30/53 patients  
158 (57%) with available bone marrow evaluation. Among the other patients, 18 had WM and 5  
159 patients had non-WM lymphoplasmacytic lymphoma. Thirty-four patients were treated with R  
160 and thirty with ICT, including 13 (43%) with DRC, 13 (43%) with FR, 3 (10%) with FCR and  
161 1 (3%) with BR.

### 162 **Modified Rankin Scale outcome and time to new treatment**

163 The median follow-up was 5 years [IQR 3.9–6.4] for the whole cohort and was longer for the  
164 ICT group (6.6 years) than for the R group (4 years). The incidence of the first mRS  
165 improvement was statistically different between the ICT group and the R group (HR = 2.41  
166 CI95% [1.10, 5.28], p = 0.023). Twelve months after treatment initiation, 46% (CI95% [26;  
167 62]) of patients had mRS improvement in the ICT group versus 18% (CI95% [2; 26]) in the R  
168 group (**Fig. 1**). In addition, the mean change of mRS between start of treatment and 12

169 months was  $-0.64$  in the ICT group versus  $-0.15$  in the R group ( $p = 0.036$ ) (**Fig. 2**). At 3  
170 years, 57% (CI95% [35; 72]) of patients had mRS improvement in the ICT group vs 30%  
171 (CI95% [11; 45]) in the R group. Median time to first mRS improvement was 25.2 months  
172 (CI95% [8.4; NR]) in the ICT group but it was not reached in the R group as less than 50% of  
173 patient had a mRS improvement. For responder patients, the median time to first response was  
174 8 months [IQR 6–10] in the ICT group versus 13 months [IQR 9–29] in the R group. After  
175 adjustment on baseline mRS score and the type of onset, incidence of the first mRS  
176 improvement was no longer significant between ICT and R groups (HR = 1.34, CI95% [0.58 ;  
177 3.12]).

178 At 5 years, 36% (CI95% [11; 45]) of ICT group patients have started a new line of treatment  
179 or died versus 39% (CI95% [12; 57]) of R group patients ( $p=0.675$ ) (**Fig. 3**). Of note, 5  
180 patients, all in the ICT group, continued to decrease their mRS after the first response. The  
181 mRS profile of each patient over time is reported in **Fig. 4**.

#### 182 **Other outcomes**

183 Twelve months after treatment initiation, electrophysiological improvement occurred in 22/52  
184 patients (42%) and its rate was higher in the ICT group (65%) vs the R group (24%) ( $p =$   
185  $0.007$ ). The electrophysiological improvement was concordant with the clinical mRS  
186 improvement in 88% of cases (**Fig. 5A**). Finally, decreases in anti-MAG and IgM were  
187 observed respectively in 27/39 (69%) and 19/48 (40%) patients, and we did not observe any  
188 statistical association between biological and mRS responses (**Fig. 5B-C**). Indeed, mRS  
189 improvement occurred in only 41% of patients with IgM decrease and in 32% of patients with  
190 anti-MAG decrease.

#### 191 **Tolerance**

192 The ICT regimen was associated with higher adverse events including all grades: 62% in the  
193 ICT group versus 15% in the R group ( $p<0.01$ ), but no toxic death was reported (**Table 3**).  
194 Rituximab-related infusion reactions were all classified as grade 1–2 and occurred in 6% of  
195 the patients. Grade 3–4 cytopenia and nausea/vomiting occurred, respectively, in 5 and 1  
196 patients, all in the ICT group. Infectious complications were reported in 4 patients in the ICT  
197 group versus 1 in the R group. They included 3 bacterial infections 1 septic shock, 1 febrile  
198 neutropenia and 1 parvovirus B19 infection (1 patient experienced 2 different infectious  
199 adverse events). Notably, 1 patient in the R group developed, after the fourth R injection, a  
200 grade 4 non-viral cytolytic hepatitis associated with neurological flare. Modified RS increased



201 from 1 to 4 and the patient temporarily required a wheelchair. In parallel, EMG and anti-  
202 MAG antibody assays worsened. The patient gradually recovered his baseline clinical  
203 condition 9 months later. Finally, 1 patient in the ICT group died from secondary acute  
204 leukaemia diagnosed 5 years after treatment (DRC and then FR).

205

## 206 **DISCUSSION**

207 Here, we report the outcomes of the largest cohort of anti-MAG neuropathy patients treated  
208 with ICT or R monotherapy. As expected, clinical characteristics assessed with mRS were  
209 different in the 2 treatment groups as follows: patients in the ICT group were more disabled  
210 than those in the R group. Indeed, in our centre, patients with severe or rapidly progressive  
211 neuropathy are more prone to be treated with ICT as a result of our previous experiences. (16)  
212 We assume that there is a major bias when comparing the efficacy of 2 treatment types but it  
213 reflects the heterogeneous presentation of the disease and the complexity of randomized trials  
214 in rare patient populations. Nevertheless, the time between onset of neuropathy and treatment  
215 initiation was similar between the 2 groups. In our cohort, the response rate at 1 year was  
216 higher (46% vs 18%) and the time to response (8 vs 13 months) shorter in the ICT group  
217 compared to the R group. In case of rapid neurological worsening with severe symptoms, a  
218 fast response is of great interest because, while waiting for the treatment to take effect,  
219 patients continue to become disabled, and the consequences may be irreversible. In the case of  
220 very slow disease progression, the patients may develop secondary axonal changes with loss  
221 of neurons. As a result, they are less likely to respond than patients with more recent disease,  
222 suggesting that, as previously noted by other authors, (19–21) a well-tolerated treatment such  
223 as R monotherapy may be proposed earlier during the disease progression in this slow  
224 context. Of note, ICT benefit was no longer significant in multivariate analysis. Taking into  
225 account confusion factors is useful in retrospective analysis. In rare patients population where  
226 randomized trials are not possible, estimating an hazard ratio at 1.34 may be clinically  
227 interesting without having the necessary power to be significant in the study. However, we  
228 cannot exclude that the effect of ICT vs. R is inferior due to residual confusion.

229 One way to improve treatment efficacy without adding adverse effects may be the use of new  
230 drugs targeting B cells, such as Bruton Tyrosine Kinase inhibitor (BTKi), but very few data  
231 are available in the specific context of anti-MAG neuropathy. In the study by Treon et al., 9  
232 patients received ibrutinib for progressive neuropathy, 3 of whom had anti-MAG antibodies.

233 (22) Subjective improvement occurred in 5 patients and 4 remained stable. In a subsequent  
234 study, 4 patients with neuropathy were treated with ibrutinib: 2 had subjective improvement  
235 and 2 remained stable. (23) More recently, ibrutinib demonstrated objective improvement  
236 occurring early in the first 3 months in 3 patients with anti-MAG neuropathy. (24) These  
237 results suggest that BTKi should be considered for anti-MAG neuropathy patients in future  
238 clinical trials and that the delay of improvement may be short.

239 One concern with anti-MAG neuropathy is that international consensus on assessing response  
240 to treatment is still lacking and clinical evaluation is difficult because of inadequate scores.  
241 Rankin and ONLS scores are disability scales and cannot effectively capture small functional  
242 changes that can greatly impact quality of life. The only-well defined sensory score available  
243 in clinical trials is the INCAT sensory score, but it is insufficiently sensitive to detect the  
244 small functional changes or sensory improvement concerning paraesthesia or pain for  
245 example. (25,26). Also, it highlighted that we probably underestimated the clinical impact of  
246 treatment because of lack of sensitivity of the neurological score and that we need to develop  
247 more sensitive scores. On the biological side, disease markers may not be suitable for  
248 assessing treatment efficacy. Indeed, we confirmed that anti-MAG antibody evolution was not  
249 correlated to the clinical response. (27,28) A possible explanation for this observation is that  
250 differences in the anti-MAG antibody titre are no longer detectable above a certain threshold.  
251 We cannot detect changes in patients with anti-MAG titres  $\geq 70,000$  BTU at baseline.  
252 Moreover, the plasma anti-MAG antibody titre does not reflect its binding capacity in the  
253 nerve tissue and does not inform on its affinity. This is why anti-MAG antibody titre is of  
254 crucial interest for demyelinating neuropathy diagnosis but not for treatment evaluation.  
255 Similarly, we did not find a correlation between the IgM response and the clinical response.  
256 This may be explained in part by the low level of IgM monoclonal gammopathy that do not  
257 allow a correct assessment of peak reduction after treatment.

258 Finally, different treatment options were used according to the successive WM international  
259 guidelines. Purine-analogs based regimens were frequently used at the beginning of the  
260 twenties but are less used because of the risk of long-lasting cytopenia and myelodysplasia.  
261 (29) DRC is effective, well tolerated and is one of the most used treatment option. (11,30)  
262 More recently, bendamustine plus rituximab have demonstrated a superior overall responses  
263 and progression-free survival with superior time to best response compared to DRC and BDR  
264 (bortezomib plus dexamethasone plus rituximab). (31,32) Thus, we recommend the use of

265 alkylating based regimen in aggressive anti MAG neuropathy: BR in fit patients, and DRC in  
266 less fit or unfit patients .

267 In conclusion, our data suggest that treatment of anti-MAG neuropathy patients can be  
268 adapted to the heterogeneous clinical presentations and that ICT can be used to treat severe or  
269 rapidly progressive neurological symptoms in order to obtain a higher response rate with a  
270 shorter time to response.

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278 V.M., K.V., D.R-W., V.L. and M.B. took care of the patients. P.G-D. and L.M. performed  
279 immunochemistry analysis, T.N. collected data, A.B. and L.B. performed statistical analysis,  
280 T.N., M.B., L.B., D.R-W. and V.L. wrote the manuscript, all authors reviewed the  
281 manuscript.

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## 380 TABLES

381 Table 1. Modified Rankin Scale.

Scale	Symptoms
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk and attend to bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Death

382

383 Table 2. Baseline clinical and biological characteristics of the patients before treatment.

Characteristic	Total	ICT	Rituximab	P value
No. of patients	64	30	34	
Median age [IQR]	63 [55-69]	63 [57-72]	62 [54-68]	0.641
Gender, n. (%)	Male: 35 (55) Female: 29 (45)	Male: 19 (63) Female: 11 (37)	Male: 16 (47) Female: 18 (53)	0.192
Underlying hematological malignancy* (n=53), n. (%)				0.131
- IgM MGCS	30 (57)	17 (63)	13 (50)	
- WM	18 (34)	6 (22)	12 (46)	
- Other lymphoproliferative disorder	5 (9)	4 (15)	1 (4)	
Clinical presentation, n. (%)				
- Sensory deficit	53 (83)	27 (90)	26 (77)	0.152
- Paresthesia/ dysesthesia	45 (70)	15 (50)	30 (88)	<b>0.001</b>
- Ataxia	43 (67)	26 (87)	17 (50)	<b>0.002</b>
- Pain	33 (52)	12 (40)	21 (62)	0.082
- Motor deficit	25 (39)	19 (63)	6 (18)	<b>&lt;0.001</b>
Median time between neuropathy onset and treatment initiation, years [IQR]	4.3 [2.1-7.4]	4.2 [1.8-7.2]	4.8 [2.4-9.5]	0.1563
Type of onset, n. (%)				<b>0.005</b>
- Acute/ Sub-acute	12 (19)	10 (33)	2 (6)	
- Chronic	52 (81)	20 (67)	32 (94)	
Modified Rankin Scale				<b>0.001</b>
- Median [IQR]	2 [1-2]	2 [2-3]	1 [1-2]	
- mRS 1-2 (%)	50 (78)	18 (60)	32 (94)	
- mRS 3-4 (%)	14 (22)	12 (40)	2 (6)	
Spike IgM level, g/L [IQR]	4 [3-4]	6 [5-8]	4 [3-8]	<b>&lt;0.001</b>
Kappa isotype, n. (%)	51 (81)	25 (83)	26 (79)	0.202
Anti-MAG titer				
- >70,000 BTU, n (%)	31(48)	16 (53)	15 (44)	0,462

- BTU [IQR]	32,900 [23,400-43,000]	40,600 [33,500-45,850]	23,700 [20,250-41,012]	<b>0.041</b>
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384

385 **Abbreviations.** ICT, immunochemotherapy; No., number; MGCS, monoclonal gammopathy  
 386 of clinical significance; mRS, modified Rankin Scale.

387 \*Underlying hemopathy was assessed with bone marrow evaluation and was available for  
 388 n=53 patients. Acute delay of degradation means  $\leq 3$  months, sub-acute between 3 and 6

	Overall		ICT		Rituximab	
	Any Grade	Grade 3 or higher	Any Grade	Grade 3 or higher	Any Grade	Grade 3 or higher
Adverse events						
Infusion reaction	4	0	2	0	2	0
Flare effect	1	1	0	0	1	1
Infectious complication	6	1	5	1	1	0
Anemia	0	3	0	3	0	0
Thrombocytopenia	3	1	3	1	0	0
Neutropenia	3	2	3	2	0	0
Aplasia	1	1	1	1	0	0
Nausea, vomiting	4	1	4	1	0	0
Hepatitis	0	1	0	0	0	1

389 months, progressive > 6 months from the diagnosis.

390 **Table 3. Treatment-induced toxicities.**

391

392

Secondary malignancy	NS	1	NS	1	NS	0
Toxic death	NS	0	NS	0	NS	0

393 **Abbreviations.** ICT, immunochemotherapy; NS: not suitable.

394

395 **FIGURE LEGENDS**

396 **Figure 1. Incidence functions of mRS response.** Modified RS response was defined as a  
 397 decrease  $\geq 1$  point under treatment. Purple line denotes patients treated with  
 398 immunochemotherapy (ICT), green line denotes patients treated with rituximab alone (R).

399 **Figure 2. Mean modified Rankin Scale at baseline and 12 months after treatment**  
 400 **initiation.** Red lines denote mRS mean, bold lines denote mRS median.**Figure 3. Probability**  
 401 **of survival without a new treatment was started.** Purple line denotes patients treated with  
 402 immunochemotherapy (ICT), green line denotes patients treated with rituximab alone (R).

403 **Figure 4. Modified Rankin Scale profile of each patient under and after treatment. A.**  
 404 **Immunochemotherapy (ICT) group, B. Rituximab (R) group.** Vertical blue (for R group) and  
 405 red (for ICT group) dotted lines denote the time point of 12 months after treatment initiation.

406 **Figure 5. Concordance between mRS response and other outcomes. A. EMG change, B.**  
 407 **Anti-MAG change, C. IgM change.** The EMG change was reported according to Lunn and  
 408 Nobile-Orazio (5) (improvement, stability or worsening). The anti-MAG change was defined  
 409 as a decrease in case of  $\geq 25\%$  titer decrease, an increase in case of  $\geq 25\%$  titer increase and a  
 410 stability in the other cases. The IgM change was defined as a decrease in case of  $\geq 25\%$  level  
 411 decrease, an increase in case of  $\geq 25\%$  level increase and a stability in the other cases. The x  
 412 axis denotes the neurological responder patients according to mRS improvement (yes) or not  
 413 (no). The y axis denotes the frequency of improvement or increase (yellow color), stability  
 414 (orange color) and worsening or increase (red color) according to the other parameters.