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► **To cite this version:**

Thomas Nivet, Amandine Baptiste, Lisa Belin, Pascale Dalbin, Caroline Algrin, et al.. Immunochemotherapy versus rituximab in anti-MAG neuropathy: a report of 64 patients. *British Journal of Haematology*, 2022, 198 (2), pp.298-306. 10.1111/bjh.18202 . hal-03643293

HAL Id: hal-03643293

<https://hal.sorbonne-universite.fr/hal-03643293v1>

Submitted on 15 Apr 2022

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

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17 **Running heads:** Immunochemotherapy in anti-MAG neuropathy.

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20 **Data sharing statement:** All data were linked and shared at Department of Haematology,
21 Pitié-Salpêtrière Hospital. External users with a formal analysis plan can request access to the
22 data to Department of Haematology.

23 **Word count:** abstract: 198 words, main text 2999 words, Figures: 5, Tables: 3

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 (≤ 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 mg/m^2 day 1) plus oral
103 cyclophosphamide (300 mg/m^2 day 1 to 5) (DRC), or oral fludarabine (40 mg/m^2 day 1 to 3)
104 plus oral cyclophosphamide (250 mg/m^2 day 1 to 3) plus R (375 mg/m^2 day 1) (FCR), or oral
105 fludarabine (40 mg/m^2 day 1 to 5) plus R (375 mg/m^2 day 1) (FR), or bendamustine (90

106 mg/m² day 1 and 2) plus R (375 mg/m² day1) (BR). In the R group, R was given: 375 mg/m²
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 ≥ 1 , stabilization as stable mRS, and progression as mRS
111 increase ≥ 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.

271 **Acknowledgments.** This study was supported by grants from INCA-DGOS-Inserm_12560
272 (SiRIC CURAMUS is financially supported by the French National Cancer Institute, the
273 French Ministry of Solidarity and Health and Inserm with financial support from ITMO
274 Cancer AVIESAN).

275 **Conflict of interest.** None.

276 **Funding statement.** No funding.

277 **Authorship statement.** V.L. and M.B designed the research study, T.N., C.A., S.C., T.L.,
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.

282

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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)	0.001
- Ataxia	43 (67)	26 (87)	17 (50)	0.002
- Pain	33 (52)	12 (40)	21 (62)	0.082
- Motor deficit	25 (39)	19 (63)	6 (18)	<0.001
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. (%)				0.005
- Acute/ Sub-acute	12 (19)	10 (33)	2 (6)	
- Chronic	52 (81)	20 (67)	32 (94)	
Modified Rankin Scale				0.001
- 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]	<0.001
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]	0.041
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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 ≤ 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 ≥ 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.