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To cite this version:

Julie Mankikian, Agnès Caille, Martine Reynaud-Gaubert, Marie-Sara Agier, Julien Bermudez, et al.. Rituximab and mycophenolate mofetil combination in patients with interstitial lung disease (EVER-ILD): a double-blind, randomised, placebo-controlled trial. European Respiratory Journal, 2023, 61, pp.2202071. 10.1183/13993003.02071-2022 . hal-04113217v1

HAL Id: hal-04113217

https://univ-tours.hal.science/hal-04113217v1

Submitted on 22 Jun 2023 (v1), last revised 26 Sep 2023 (v2)

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Rituximab and mycophenolate mofetil combination in patients with interstitial lung disease (EVER-ILD): a double-blind, randomised, placebo-controlled trial

Julie Mankikian, Agnès Caille, Martine Reynaud-Gaubert, Marie-Sara Agier, Julien Bermudez, Philippe Bonniaud, Raphael Borie, Pierre-Yves Brillet, Jacques Cadranel, Isabelle Court-Fortune, Bruno Crestani, Marie-Pierre Debray, Emmanuel Gomez, Anne Gondouin, Sandrine Hirschi-Santelmo, Dominique Israel-Biet, Stéphane Jouneau, Karine Juvin, Julie Leger, Mallorie Kerjouan, Charles-Hugo Marquette, Jean-Marc Naccache, Hilario Nunes, Laurent Plantier, Grégoire Prevot, Sébastien Quetant, Julie Traclet, Victor Valentin, Yurdagul Uzunhan, Lidwine Wémeau-Stervinou, Theodora Bejan-Angoulvant, Vincent Cottin, Sylvain Marchand-Adam, on behalf of the EVER-ILD investigators and the OrphaLung network.

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Running title: Rituximab in nonspecific interstitial pneumonia

Word count: 3800

Tables/figures: 3/4 (plus supplementary tables/figures)

References: 30

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Summary

Background

Standard of care for interstitial lung disease (ILD) with a nonspecific interstitial pneumonia (NSIP) pattern proposes mycophenolate mofetil (MMF) as one of the first step therapies while rituximab is used as rescue therapy.

Methods

In a randomised, double blind, two-parallel group, placebo-controlled trial (NCT02990286), patients with connective tissue disease-associated ILD or idiopathic interstitial pneumonia (with or without autoimmune feature) and a NSIP pattern (defined on NSIP pathological pattern or on integration of clinico-biological data and a NSIP-like HRCT pattern) were randomly assigned in a 1:1 ratio to receive rituximab (1000 mg) or placebo on day 1 and day 15 in addition to MMF (2 g daily) for six months. The primary endpoint was the change in percent of predicted forced vital capacity (FVC) from baseline to 6 months analysed by a linear mixed model for repeated measures analysis. Secondary endpoints included progression-free survival (PFS) up to 6 months and safety.

Findings

Between January 2017 and January 2019, 122 randomised patients received at least one dose of rituximab (n=63) or placebo (n=59). The least-squares mean change from baseline to 6 months in FVC (% predicted) was +1.60 (SE 1.13) in the rituximab+MMF group and -2.01 (SE 1.17) in the placebo+MMF group (between-group difference, 3.60 [95% CI 0.41 to 6.80]; p=0.0273). PFS was better in the rituximab+MMF group (crude HR 0.47 [95%CI 0.23 to 0.96]; p=0.03). Serious adverse events occurred in 26 patients of the rituximab+MMF group (41%) and in 23 of the placebo+MMF group (39%). Nine infections were reported in the

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99 rituximab+MMF group (five bacterial infections, 3 viral infections, 1 other) and four bacterial

100 infections in the placebo+MMF group.

101 **Interpretation**

102 Combination of rituximab and MMF was superior to MMF alone in patients with ILD and a

103 NSIP pattern. The use of this combination must consider the risk of viral infection.

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105 **Introduction**

106 Non-specific interstitial pneumonia (NSIP) is a pathological pattern of ILD with a temporally
107 uniform interstitial process with varying proportions of interstitial inflammation and
108 fibrosis[1, 2]. Although lung biopsy is required to formally diagnose ILD with a NSIP pattern,
109 most often the risks of lung biopsy outweigh the benefits of establishing a secure diagnosis,
110 and the diagnosis relies on the integration of clinical, biological and HRCT data in a
111 multidisciplinary discussion (MDD) meeting. In the absence of pathological information, the
112 integration of available data into a presumptive diagnosis of ILD with a NSIP-like HRCT
113 pattern (defined as basal predominant reticular abnormalities with peri-bronchovascular
114 extension and subpleural sparing, associated with ground-glass attenuation[2, 3]) can
115 facilitate management decisions for the use of immunomodulatory therapy.

116 A NSIP pathological pattern is a common feature of ILD associated with connective tissue
117 diseases (CTD-ILD)[1], idiopathic interstitial pneumonia with autoimmune features (IPAF)[4]
118 and some idiopathic ILD (iILD)[5]. In the absence of specific clinical trials, current knowledge
119 on the treatment of ILD with a NSIP pattern was obtained in multicentre clinical trials in
120 scleroderma-related ILD (SSc-ILD)[6, 7], where NSIP is the most common ILD pattern.
121 Immunosuppression with mycophenolate mofetil (MMF) is presently the most common first-
122 step therapy[8] in progressive CTD-ILD, and by extension in interstitial pneumonia with
123 autoimmune features (IPAF) and some patients with idiopathic ILD with a NSIP pattern.
124 Mycophenolic acid induces apoptosis of T- and B-lymphocytes and inhibits vascular smooth
125 muscle proliferation, myofibroblast differentiation, and adhesion of circulating inflammatory
126 cells to endothelial cells[9]. In patients with some CTDs who do not respond to first-line
127 treatment, rituximab can be used as a rescue therapy [10, 11]. Rituximab is a chimeric
128 monoclonal antibody that targets the CD20 protein and induces cell death of pre-B and

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129 mature B-lymphocytes. There is a rationale for rituximab use in ILD with a NSIP pattern,
130 since immunoglobulin deposits and lymphocytes CD20+ infiltrates are observed in patients
131 with a NSIP pathological pattern [12]. We hypothesized that the association of MMF and
132 rituximab could have an additive efficacy in patients with ILD with a NSIP pattern.
133 Therefore, we conducted the EVER-ILD phase 3, randomised controlled trial to assess the
134 efficacy and safety of rituximab plus MMF versus MMF alone in patients with ILD and a NSIP
135 pathological pattern or NSIP-like HRCT pattern.
136

137 ## Methods

138 **Trial design**

139 This was a multicentre, randomised, double blind, two-parallel group, placebo-controlled,
140 superiority trial. The methods of this study have been previously described[13] (appendix
141 pp23-89). The trial was conducted at 17 academic French centres specialised in rare
142 pulmonary diseases including ILDs, all being part of the OrphaLung and RespiFIL (Filière
143 Santé Maladies Respiratoires Rares) networks.
144 All trial aspects were conducted in accordance with the ethical principles of the Good Clinical
145 Practice guidelines and the Declaration of Helsinki, in compliance with French laws. This trial
146 is registered with ClinicalTrials.gov (NCT02990286).

147 **Participants**

148 Eligible patients were aged ≥18 and had a diagnosis of CTD-associated ILD or idiopathic
149 interstitial pneumonia. Two idiopathic interstitial pneumonia groups were individualized :
150 1/interstitial pneumonia with autoimmune features (IPAF) categorized as a patient group
151 that exhibit evidence of autoimmunity without meeting criteria for a defined connective
152 tissue disease and 2/interstitial pneumonia without an identified cause or autoimmunity

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153 (iILD). The consensus diagnosis of ILD with a NSIP pattern was defined by the local MDD
154 based on a NSIP pathological pattern (ILD with a NSIP pathological pattern) when available
155 or on integration of available clinico-biological data and a NSIP-like HRCT pattern (ILD with a
156 NSIP-like HRCT pattern). NSIP-like HRCT pattern was defined as basal predominant reticular
157 abnormalities with peri-bronchovascular extension and subpleural sparing, associated with
158 ground-glass attenuation[2, 3].
159 Patients were eligible if they did not respond to, or relapsed after, a first line of
160 glucocorticoids and/or immunosuppressive treatment (appendix pp 5).
161 Main reasons for exclusion were significant respiratory disorders other than CTD-ILD, IPAF or
162 iILD, other severe or unstable medical condition (as per investigator's judgement), and a
163 pattern of typical or possible[14]/probable[15] usual interstitial pneumonia (UIP). The
164 presence of significant pulmonary hypertension proven by right heart catheterization was an
165 exclusion criterion. However, patients with a possible elevated pulmonary arterial pressure
166 (systolic pulmonary arterial pressure >=45 on echocardiography) not confirmed by right
167 heart catheterization could be included. When lung biopsy was available, patients with a
168 histological pattern other than NSIP were excluded. Full inclusion and exclusion criteria are
169 described in appendix pp 42-44.
170 After a screening period of up to 30 days, eligible patients were randomly assigned by the
171 investigator via a centralised web-based interactive response system (CSOnline) to receive
172 rituximab (1000 mg) or placebo on day 1 and day 15 in addition to MMF (2 g daily) for six
173 months. The 2 g daily dose of MMF was selected to limit the risk of infection with combined
174 immunosuppression. Allocation sequences were generated in a 1:1 ratio using a computer-
175 generated randomisation schedule by an independent statistician, not involved in patient
176 recruitment or follow-up. Randomisation was stratified on type of ILD groups (differentiated

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177 CTD-ILD or IPAF vs. iILD) and on FVC% predicted at inclusion (<50% vs ≥50%). Randomisation
178 was done through permuted blocks. Blinding and dosing administration can be found in the
179 supplementary material (appendix pp 6, 47 and 63).

180 **Outcomes**

181 The primary efficacy endpoint was change in FVC (percent of predicted, absolute FVC %)
182 from baseline to 6 months. FVC was measured within each study centre in a standardized
183 manner according to ATS/ERS recommendations[16] and ECCS reference equations by
184 technicians blinded to study treatment group[17].

185 Secondary efficacy endpoints included progression free survival (PFS) measured over the 6
186 month follow-up, changes from baseline to 6 months in the SF-36 v1.3 quality of life
187 questionnaire, cumulative doses of glucocorticoids over the 6 month treatment period,
188 changes from baseline to 6 months in FVC (ml), and changes from baseline to 6 months in
189 visual analogic scales (VAS, 0-10 cm) for dyspnea and cough, DLCO in % of predicted, 6-
190 minute-walk test, autoantibodies, blood CD19 lymphocytes count, and serum
191 gammaglobulins. PFS was defined as the time to a first acute exacerbation or FVC absolute
192 decline ≥ 10 predicted percentage points, MMF withdrawal or registration on a pulmonary
193 transplantation list or death, whichever occurred first. An acute exacerbation was defined by
194 (1) progressive dyspnea over 1 month or less; (2) new pulmonary infiltrates on chest
195 radiography or computed tomography, and (3) the absence of an overt underlying cause of
196 rapid deterioration. Changes from baseline to 6 months in HRCT chest images were assessed
197 by two thoracic radiologists with expertise in ILDs, who scored the extent of ILD and the
198 severity of traction bronchiectasis (appendix pp6). Rituximab pharmacokinetics were
199 secondary outcomes but will be reported separately. Safety was assessed by clinical and

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200 laboratory parameters and the recording of adverse events, as coded with the use of the
201 Medical Dictionary for Regulatory Activities, version 23. The pharmacovigilance experts
202 adjudicated the adverse events and determined whether or not they were related to the
203 study treatment. They were blinded to treatment arm assignment except for potentially
204 related unexpected serious events where they requested the unblinding (i.e. for 2 SUSARs).
205 There were no exploratory endpoints in this trial.

206 **Statistical analysis**

207 Assuming a power of 90%, a 5% two-sided type I error rate and anticipating an extreme 10%
208 drop-out rate, 122 patients (61 per group) were needed to show a 5% between-group
209 difference in the change of FVC percent of predicted value at 6 months, based on a common
210 standard deviation for FVC change between baseline and 6 months of 8%[18]. In case a
211 randomised patient did not receive any dose of the allocated treatment, we planned to
212 randomise additional patients until we reached our target sample size of 122 patients.
213 Efficacy and safety analyses included all randomly assigned participants who received at last
214 one dose of rituximab or placebo on day 1 of the treatment period. Patients who withdrew
215 consent to study participation were not included in the analysis as required by French law.
216 We used two-sided significance tests with a type I error of 5%.
217 For the primary analysis, we used a linear mixed model for repeated measures to compare
218 differences between study groups in the slope of FVC measurements over the 6 months
219 study period (time points at baseline, 3 and 6 months). The model included treatment group,
220 visit and treatment-by-visit interaction as fixed-effects. We used a model with random
221 individual intercepts and slopes over time. The treatment effect was assessed using the
222 treatment-by-visit interaction. This model assumes data are missing at random, and missing

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223 data were not imputed for the primary analysis. For patients who did not attend all the study
224 visits, we used all available FVC measurements in the primary analysis. We performed
225 different imputation sensitivity analyses to assess the impact of missing data and the
226 robustness of the treatment effect under different assumptions for missing data (appendix
227 Table S8 Fig. S2 pp 19 and 22).
228 A priori subgroups were defined by stratification variables for randomisation: ILD groups
229 (CTD-ILD or IPAF vs. iILD) and FVC in % predicted value at inclusion (< 50% vs. ≥ 50%). We
230 also performed post hoc exploratory subgroup analyses (appendix pp 7)
231 For secondary efficacy endpoints, all data from baseline to 6 months were used without
232 imputation of values for patients who discontinued early. We reported p values with no
233 adjustment for multiplicity and for descriptive purposes only. The predicted change in FVC in
234 ml between baseline and 6 months was analysed using the same method as for the primary
235 endpoint. Progression-free survival was described by Kaplan-Meier curves and compared
236 between study groups using a log-rank test and unadjusted Cox proportional hazards model.
237 A Cox proportional hazards model with *post-hoc* adjustment on stratification variables was
238 also fitted. Between-group comparisons for absolute changes between baseline and 6
239 months in continuous outcomes were performed with Student's *t*-tests.
240 Analyses were performed using SAS software version 9.4 (SAS Institute) and R software
241 version 4.0.3 was used for creating some of the figures[19].
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243 **Results**

244 Between January 26, 2017 and January 25, 2019, 126 patients with ILD and a NSIP
245 pathological pattern or a NSIP-like HRCT pattern were randomised (Figure 1). Three patients
246 did not receive the intervention and 1 patient withdrew consent. Among the 122 patients
247 who received at least one dose of the assigned treatment, 63 were in the rituximab group
248 and 59 were in the placebo group. 60 (95%) and 59 (94%) of 63 patients in the rituximab
249 group and 58 (98%) and 55 (93%) of 59 in the placebo group completed the 3-month and 6
250 month-visit, respectively.

251 The baseline characteristics and previous treatments of the patients were similar in the two
252 treatment groups (Table 1 and appendix table S1 p 8). In the overall population, mean age
253 was 66.1 (SD 12.0) years. At baseline, mean FVC % predicted was 66.7 (SD 21.5) in the
254 rituximab + MMF group and 70.2 (SD 22.5) in the placebo + MMF group, and % predicted
255 DLCO was 40.1 (SD 13.5) and 38.6 (SD 14.8), respectively.

256 The patients were divided by MDD in investigator centres into the CTD group (n=43, 35%),
257 the IPAF group (n=36, 30%) and the iILD group (n=43, 35%). Within the CTD-ILD group, 23
258 patients (53%) were diagnosed with systemic sclerosis, 8 (19%) with inflammatory myositis,
259 7 (16%) with Sjögren syndrome, 3 (7%) with rheumatoid arthritis and 2 (5%) with mixed
260 connective tissue disease (appendix table S2, p 9). Surgical lung biopsies confirming definite
261 NSIP were available for 10 patients (16%) in the rituximab + MMF group and 5 patients (8%)
262 in the placebo group. One patient in the IPAF group had a pathological diagnosis of
263 desquamative interstitial pneumonia and was wrongly included. For one patient, biopsy was
264 non-contributory. In this patient grouped with patients without lung biopsies (n=106), the
265 concordance in the determination of the NSIP-like HRCT pattern was 86% between the local
266 MDD and a posteriori centralized review by 2 thoracic radiologists (appendix table S3 p 10).

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267 Three patients did not receive the second infusion of rituximab (2 for anaphylactoid
268 reactions and one because of a cardiac procedure) and one patient did not receive the
269 second infusion of placebo (ILD progression and death). Mycophenolate mofetil
270 discontinuation before 6 months was more frequent in the rituximab + MMF group (14
271 patients, 22%) than in the placebo + MMF group (9 patients, 15%) (appendix table S4, p 11).
272 Linear mixed model analysis showed a significant difference in absolute change from
273 baseline in FVC % predicted between groups at 6 months. The least-squares mean (LSM)
274 change from baseline to 6 months in FVC % predicted was +1.60 (SE 1.13) in the rituximab +
275 MMF group compared with -2.01 (SE 1.17) in the placebo + MMF group (between-group
276 difference, 3.60 [95% CI 0.41 to 6.80]; p=0.0273; figure 2, table 2). Results were replicated
277 when adjusted for stratification variables (FVC % predicted at baseline and type of disease)
278 (table 2).
279 Variation of FVC in ml up to 6 months was consistent with the result of the primary outcome
280 (appendix figure S1, p 18). LSM change from baseline to M6 was +41 ml (SE 30) in the
281 rituximab + MMF group and −59 ml (SE 31) in the placebo + MMF group (between-group
282 difference, 100 ml [95% CI 15 to 185], p=0.0207).
283 Progression-free survival (PFS) was greater in the rituximab + MMF group than in the
284 placebo + MMF group (crude hazard ratio [HR] 0.47 [95% CI 0.23 to 0.96]; p=0.03; Figure 3).
285 A greater number of patients presented investigator-reported exacerbation as first event of
286 PFS in the placebo + MMF group than in the rituximab group + MMF (respectively 8 patients
287 vs 2) (appendix table S5, p 12). Results for the *post-hoc* adjusted Cox proportional hazards
288 are provided in appendix table S6, p 13).
289 No between-group differences in change from baseline to 6 months were noted for the
290 physical composite score and the mental composite score of the SF36 questionnaire

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291 (appendix, table S7, p 14-15). The mean cumulated glucocorticoid dose over the 6 months of
292 the study was 1862 mg (SD 1756) in rituximab + MMF group and 2314 mg (SD 2082) in
293 placebo + MMF group (p=0.20). No significant between group difference was observed in
294 change from baseline to 6 months in 6-minute walk distance, DLCO, dyspnea and cough, in
295 HRCT ILD extent nor bronchiectasis scores. Decrease in CD19 counts from baseline to 6
296 months was significantly greater in the rituximab + MMF group than in the placebo + MMF
297 group. Change in gammaglobulin serum levels from baseline to 6 months did not differ
298 between groups. Change in autoantibody status between baseline and 6 months did not
299 differ between groups (appendix, table S7 and S8, p14-16).
300 Post hoc sensitivity analyses of the primary outcome with different methods for handling
301 missing data yielded P values ranging from 0.02 to 0.11 and were consistent with the results
302 of the primary analysis (appendix, table S9, figure S2, pp 17, 20). These findings showed that
303 the primary results were robust and were not influenced by alternative assumptions about
304 missing data.
305 Results of the prespecified and post hoc subgroup analyses for the percentage predicted FVC
306 are presented in figure 4. Rituximab and MMF combination demonstrated a consistent
307 treatment effect on the percentage predicted FVC across the majority of subgroups. The
308 benefit of combination could be less in the subgroups of patients who have walked less than
309 150m, with a systolic pulmonary arterial pressure > 45 mmHg, with oxygen therapy > 10H/d
310 or with UIP or indeterminate HRCT pattern after posteriori centralized review.
311 Overall, 54 patients in the rituximab + MMF group (86%) and 57 in the placebo + MMF group
312 (97%) experienced at least one adverse event (table 3). A total of 36 serious adverse events
313 in the rituximab + MMF group and 33 in the placebo + MMF group were reported, with 26
314 patients (41%) and 23 patients (39%) experiencing at least one serious adverse event. More

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315 patients experienced serious adverse events considered to be related to study treatment in
316 the rituximab + MMF group compared to placebo + MMF (15 patients vs 6). Non-infectious
317 respiratory tract disorders (3 patients in the rituximab + MMF group vs 12 in the placebo +
318 MMF group), and cardiac disorders (5 patients vs 2) were reported as the most frequent
319 serious adverse events. Nine infections were reported in the rituximab + MMF group (2
320 urinary tract infections, 3 pneumonia, 2 influenzae virus infections, 1 varicella, 1 other
321 without microbiological documentation) and four infections in the placebo + MMF group (3
322 pneumonia, 1 sepsis). Infusion-related reactions were uncommon in both groups (3 patients
323 in the rituximab + MMF group and 1 in the placebo + MMF group). During the 6-month
324 follow-up period 3 deaths were reported in the rituximab + MMF group (all due to end-stage
325 respiratory failure) and 4 in the placebo + MMF group (1 infectious pneumonia with acute
326 exacerbation of fibrosis and 3 acute respiratory failure). No fatal SAEs were assessed as
327 possibly related to rituximab and MMF combination.
328
329

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330 **Discussion**

331

332 In the EVER-ILD trial, we investigated the efficacy and safety of a combination of rituximab
333 and MMF in comparison with a combination of placebo and MMF, in patients with ILD with a
334 NSIP pathological pattern or NSIP-like HRCT pattern who were previously treated with either
335 glucocorticoids or an immunosuppressive agent. Rituximab + MMF led to a significant
336 improvement in change from baseline to 6 months in FVC % predicted in comparison with
337 placebo and MMF. Progression-free survival over the 6-month study period was higher in
338 the rituximab plus MMF group. Combination of MMF and rituximab was not associated with
339 more frequent adverse events.
340 The EVER-ILD study is the first randomised, double-blind, placebo-controlled trial showing
341 that combined immunosuppressive treatment with rituximab and MMF combination is
342 beneficial in ILD with a NSIP pattern. The benefit in FVC was approximately 3.6% of the
343 predicted value and 100 mL over the 6-month study period in patients treated with the
344 combination of rituximab plus MMF. Besides improving respiratory function, rituximab and
345 MMF combination improved progression-free survival. The latter appeared to result mainly
346 from a reduced first exacerbation frequency.
347 Although the evidence was restricted to uncontrolled retrospective studies[20–23], previous
348 data suggested that combination of rituximab and MMF may be beneficial relative to MMF
349 in ILD. Narvaez et al. reported that rituximab rescue therapy used as an add-on treatment to
350 MMF improves FVC in SSc-ILD patients with non-UIP HRCT patterns[23]. While considerable
351 research effort has been devoted to idiopathic pulmonary fibrosis (IPF) and other ILDs with
352 the progressive fibrotic phenotype[24], to our knowledge the present randomised placebo-
353 controlled trial is the first to focus on ILD with a NSIP pattern.

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354 Low FVC and DLCO are significant risk factors for acute exacerbation of ILD. In the present
355 study, many patients had severe disease as 23/122 (19%) had FVC less than to 50% and
356 47/115 (41%) had DLCO less than 30% or could not perform the DLCO test. It is likely that
357 patient severity explains the high rate of patients with at least one investigator-reported
358 exacerbation and death in comparison to previous studies. In the INBUILD trial, where
359 patients with FVC <50% or with DLCO <30% or who could not perform the DLCO test were
360 excluded, the exacerbation or death rate at 1 year was 9.7%[24]. In the absence of an
361 independent committee on the clinical evaluation criteria to adjudicate on acute
362 exacerbations in EVER-ILD study, investigators may have over-reported acute respiratory
363 events as acute exacerbation.
364 The natural history of some ILDs includes gradual deterioration of respiratory function. In
365 the placebo groups of prospective studies in SSc-ILD[25], FVC decreased over the course of
366 the trial (-4.6% and -2.6% of predicted FVC at week 48 in FOCUSScED and SLS-I studies
367 respectively), and FVC decline was barely reduced in the group with immunosuppressive
368 monotherapy (-0.4% and -1% in FOCUSScED and SLS-I studies respectively)[6, 26]. Apart from
369 the EVER-ILD trial, there are few prospective studies in ILD that showed an improvement in
370 FVC. In the SLS-II study, MMF and cyclophosphamide increased FVC at 12 months compared
371 to baseline with a plateau at 24 months of +2.19% predicted value (95% CI 0.53-3.84) in the
372 MMF group[7]. In the RECITAL study which assessed rituximab compared with
373 cyclophosphamide, patients in both treatment groups had increased FVC at 24 weeks
374 (cyclophosphamide group (+99 mL [SD 329]) and the rituximab group (+97 mL [SD 234])
375 [27].
376 The safety profile of rituximab was similar to that described in previous trials[20, 23, 28]. The
377 rituximab and MMF combination was well tolerated. Patients in the rituximab plus MMF

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378 group had more frequent infections (9 patients vs 4), cardiac disorders (5 patients vs 2) and
379 infusion-related reactions (3 patients vs 1). The infections observed with the rituximab and
380 MMF combination were mainly non-serious viral infections, as previously reported with
381 rituximab[29]. An important point is that patients were enrolled in EVER-ILD prior to the
382 COVID-19 pandemic. We have no formal explanation for the tendency to greater frequency
383 of intolerance to MMF in the MMF+rituximab group compared to the MMF+placebo group.
384 Additional research may be needed to assess a potential effect of rituximab on MMF
385 pharmacokinetics.
386 The main limitation of the study concerns the diagnosis of ILD with a NSIP pattern. NSIP has
387 a pathological definition thus a formal diagnosis of NSIP requires lung biopsy. The majority of
388 our patients did not have lung biopsy after evaluation in MDD of the benefit/risk balance
389 because of the presence of a CTD or autoimmune features, because of ILD severity or the
390 presence of comorbidities, and/or because of the patient's refusal (appendix S3 pp 10). In
391 the absence of a lung biopsy, the presence of an NSIP-like HRCT pattern could be a
392 determining factor in the decision of the choice of treatment during an MDD because an
393 NSIP pathological pattern is present in 65-90% of patients with NSIP-like HRCT pattern[30].
394 The quality of the HRCT analysis becomes essential. In EVER-ILD, the concordance in the
395 determination of the NSIP-like HRCT pattern was 86% between the local MDD and a
396 posteriori centralized review by 2 thoracic radiologists. Despite this imperfect concordance,
397 sensitivity analyses for the primary endpoint with exclusion of 15 patients with UIP and
398 indeterminate HRCT pattern after the centralized review, were consistent with the results of
399 the primary analysis (Appendix table S10 pp 18). Even if the absence of lung biopsy is a
400 weakness of the pragmatic EVER-ILD study, its results can help in decision-making in patients
401 with presumptive diagnosis of ILD with a NSIP-like HRCT pattern.

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402

403 In summary, we show that treatment of ILD with a NSIP pattern with the rituximab and MMF
404 combination results in improved lung function from baseline to 6 months as measured by
405 FVC, in comparison with MMF alone. Rituximab and MMF combination might be a
406 reasonable strategy for patients with a diagnosis of ILD with a NSIP pattern in MDD. Further
407 studies are needed to evaluate the potential impact of rituximab use beyond 6 months as a
408 maintenance therapy. The rituximab and MMF combination was associated with an increase
409 in non-serious viral infections. The use of rituximab must be evaluated according to the
410 benefit/risk balance, in particular during a viral pandemic.

411

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412 **Contributors**

413 The research concept of the study was developed by SMA and TA. All authors undertook the
414 study. AC conceptualised the statistical analyses, calculated the sample size. AC and JL did
415 the statistical analysis. SMA, TA, AC and JL accessed and verified the data. All authors
416 participated in the development and finalisation of the manuscript and vouch for the trial's
417 fidelity to the protocol. All authors had full access to all the data in the study. SMA, AC, JM
418 and TA had final responsibility for the decision to submit for publication.

419

420 **Declaration of interests**

421 Stephane Jouneau has received fees, funding or reimbursement for national and
422 international conferences, boards, expert or opinion groups, research projects over the past
423 3 years from AIRB, Bellorophon Therapeutics, Biogen, Boehringer, Chiesi, Fibrogen, Galecto
424 Biotech, Gilead, LVL, Novartis, Olam Pharm, Pfizer, Pliant Therapeutics, Roche, Sanofi-
425 Genzyme, Savara.
426 Raphael Borie has received fees, funding or reimbursement for national and international
427 conferences, boards, expert or opinion groups, research projects over the past 3 years from
428 Boehringer, Roche, Sanofi- Genzyme, Savara, Chiesi outside the submitted work
429 Philippe Bonniaud reports personal fees and non-financial (reimbursement for national and
430 international conferences) support from Roche, Boehringer Ingelheim, Novartis, Sanofi and
431 non-financial support (reimbursement for national and international conferences) from
432 Chiesi and Stallergene.
433 Jean-Marc Naccache has received fees, funding or reimbursement for national and
434 international conferences, boards, expert or opinion groups, research projects over the past
435 3 years from Astra Zeneca, Boehringer Ingelheim outside the submitted work.
436 Laurent Plantier has received fees, funding or reimbursement for national and international
437 conferences, boards, expert or opinion groups, research projects over the past 3 years from
438 Astra Zeneca, Boehringer Ingelheim, Chiesi, GSK, Sanofi, Humanair, and Arair outside the
439 submitted work.

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Bruno Crestani has received fees, funding or reimbursement for national and international conferences, boards, expert or opinion groups, research projects over the past 3 years from BMS, Boehringer Ingelheim, Roche, Apellis, Sanofi, Novartis, AstraZeneca, Chiesi outside the submitted work

Marie Pierre Debray has received or reimbursement for national and international conferences, educational events over the past 3 years from Boehringer Ingelheim and Roche outside the submitted work

Lidwine Wémeau-Stervinou reports personal fees and non-financial (reimbursement for national and international conferences) support from Roche, Boehringer Ingelheim, Sanofi, BMS outside the submitted work

JC reports personal fees and non-financial support from Boehringer Ingelheim and Roche outside the submitted work.

Jacques Cadranel reports honoraria for educational events from Boehringer Ingelheim and Roche outside the submitted work

Dominique Israël-Biet reports consulting fees from Boehringer Ingelheim, honoraria for educational events from Boehringer Ingelheim and Roche, payments from Galapagos as a member of an adjudication comittee, supports for attending meetings and/or travel from Boehringer Ingelheim outside the submitted work

Vincent Cottin reports grants, personal fees and non-financial support from Boehringer Ingelheim, personal fees and non-financial support from Roche, personal fees from Celgene / BMS, MSD, CSL Behring, Galapagos, Galecto, Shionogi, Fibrogen, RedX, and PureTech, Promedior outside the submitted work.

Sylvain Marchand-Adam has received fees, funding or reimbursement for national and international conferences, boards from Boehringer Ingelheim, Roche, BMS ; Novartis; Astra Zeneca; Pfizer; GSK; Chiesi outside the submitted work.

Victor Valentin, has received fees, funding or reimbursement for national and international conferences, boards from Boehringer Ingelheim, outside the submitted work

Julie Mankikian, Agnes Caille, Martine Reynaud-Gaubert, Marie-Sara Agier, Julien Bermudez, Pierre-Yves Brillet, Isabelle Court-Fortune, Emmanuel Gomez, Anne Gondouin, Sandrine Hirschi-Santelmo, Karine Juvin, Julie Leger, Mallorie Kerjouan, Charles-Hugo Marquette, Hilario Nunes, Laurent Plantier, Grégoire Prevot, Sébastien Quetant, Julie Traclet, Yurdagul

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Uzunhan, Lidwine Wémeau-Stervinou, Theodora Bejan-Angoulvant, declare no competing interests

Data sharing

We will make anonymised individual participant data available to the scientific community with as few restrictions as feasible, while retaining exclusive use until the publication of major outcomes. Data requests from qualified researchers should be submitted to SMA (s.marchandadam@univ-tours.fr) for consideration.

Acknowledgments

We gratefully acknowledge the patients for their participation in this trial. This study was supported by a grant from the French Ministry of Health (Programme Hospitalier de Recherche Clinique) 2015. The trial protocol was written with support from a Grand-Ouest interregion support project aiming to promote and facilitate clinical research on monoclonal antibodies (MIAMIGO) and from the Pilot Centre for Therapeutic Antibodies Monitoring (PITAM-CePiBAc) of Tours University Hospital. We thank Estelle Boivin, Mathilde Husson, Elody Mureau and Magali Rehaut for their contribution in this study. The authors would like to thank the Research Coordinators from the Clinical Investigation Center of Lyon, Inserm 1407

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491 **Table 1: Demographic and baseline characteristics of study participants**

	Rituximab + MMF n_R=63	Placebo +MMF n_P=59
Sex – Female	35 (55.6)	38 (64.4)
Age (years)	64.7 (12.1)	67.5 (11.9)
BMI (kg/m²)	29.0 (5.4)	28.4 (5.2)
Years since ILD diagnosis	3.8 (4.9)	2.9 (2.7)
FVC (% predicted value)	66.7 (21.5)	70.2 (22.5)
FVC (ml), n_R=63, n_P=58	2046 (767)	1971 (724)
FEV1/FVC (%), n_R=63, n_P=57	85.7 (11.0)	86.9 (14.0)
DLCO, n_R=60, n_P=55		
Unfeasible	9 (15.0)	12 (21.8)
% of predicted value, n_R=51, n_P=43	40.1 (13.5)	38.6 (14.8)
6 MWD (m), n_R=61, n_P=55	364 (148)	325 (179)
O2 > 10h/day at baseline	13 (20.6)	17 (28.8)
Histopathologic NSIP	10 (15.8)	5 (8.5)
ILD groups		
CTD-ILD	25 (39.7)	18 (30.5)
IPAF	17 (27.0)	19 (32.2)
Idiopathic ILD	21 (33.3)	22 (37.3)
Glucocorticoids at baseline	46 (73.0)	50 (84.7)
Glucocorticoids dose at baseline (mg/d)	15 [10;20]	17.5 [10;25]
Previous treatment received for ILD*		
None**	2 (3.2)	0
Glucocorticoids alone	36 (57.1)	33 (55.9)
Immunosuppressive agent alone	2 (3.2)	0
Glucocorticoids + Immunosuppressive agent	23 (36.5)	26 (44.1)

492 Data are n (%) or mean (SD) or median [Q1;Q3]. 6MWD=6-minute walk distance. BMI=body mass index.
493 CTD=connective tissue disease. DLCO=carbon monoxide diffusing capacity. FEV_1=forced expiratory volume in 1
494 second. FVC=forced vital capacity. HRCT= High-resolution computed tomography. ILD=interstitial lung disease.
495 IPAF=interstitial pneumonia with autoimmune features. MMF=mycophenolate mofetil. NSIP=non-specific
496 interstitial pneumonia.
497 *Any previous treatments were considered and were specified in appendix table S1
498 **Patients with a contraindication to glucocorticoids

499

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500 **Table 2: Primary efficacy endpoint**

LSM change in FVC % predicted value from baseline to M6	Rituximab + MMF $n_R=63$	Placebo + MMF $n_P=59$	Between-group difference- (95% CI)	p-value
Primary analysis	1.60 (-0.63 to 3.82)	-2.01 (-4.31 ; 0.29)	3.60 (0.41 to 6.80)	0.0273
Adjusted model on stratification variables*	1.53 (-0.69 to 3.76)	-2.04 (-4.35 to 0.26)	3.58 (0.38 to 6.79)	0.0288

501 Data are least squares means with 95% CIs estimated by a mixed-effects model for repeated measures.
502 CI=Confidence interval. FVC=forced vital capacity. ILD=interstitial lung disease. MMF=mycophenolate mofetil.
503 *Stratification variables: FVC % predicted at baseline (<50% vs ≥50%) and type of ILDs (differentiated CTD-ILD
504 or IPAF vs idiopathic ILD).
505

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506 **Table 3: Summary of all AEs**

507

	Rituximab + MMF (n_R=63)	Placebo + MMF (n_P=59)
Any adverse event	54 (86)	57 (97)
Related to study treatment	36 (57)	27 (46)
Any serious adverse event	26 (41)	23 (39)
Most common serious adverse event		
Respiratory tract disorders	3 (5)	12 (20)
Infection	9 (14)	4 (7)
Cardiac disorders	5 (8)	2 (3)
Leading to discontinuation of study treatment	3 (5)	1 (2)
Fatal adverse event	3 (5)	4 (7)
Related to study treatment	15 (24)	6 (10)
Infection	9 (14)	4 (7)
Infusion related reaction	3 (5)	1 (2)

508 Data are n (%) of patient with adverse event. MMF=mycophenolate mofetil

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645 Figure 1: Enrolment and randomisation in the overall population.

646 PFTs=pulmonary function tests

647

648 Figure 2: Variation from Baseline in Forced Vital Capacity (FVC). Shown is the least squares

649 mean (LSM) change from baseline in FVC (in percent of predicted) over the 6 months trial

650 period in the rituximab + MMF group and the placebo + MMF group. The I bars indicate the

651 confidence interval (CI).

652 MMF = mycophenolate mofetil.

653

654 Figure 3: Time-to-event analyses, from baseline, for patients who PFS defined as >10%

655 absolute decline in percent predicted FVC, first acute exacerbation, MMF discontinuation for

656 disease degradation, registration on lung transplant list or death.

657 CI=confidence interval. FVC = forced vital capacity. MMF = mycophenolate mofetil. PFS =
658 progression free survival.

659

660 Figure 4: Subgroup analyses of mean change in forced vital capacity from baseline to M6.

661 BMI=body mass index. CI=confidence interval. CTD=connective tissue disease. DLCO=carbon

662 monoxide diffusing capacity. FVC=forced vital capacity. HRCT= high-resolution computed

663 tomography. ILD=interstitial lung disease. IPAF=interstitial pneumonia with autoimmune

664 features. NSIP=non-specific interstitial pneumonia. PASP= estimate pulmonary artery systolic

665 pressure using echocardiography. VAS= visual analogic scales.

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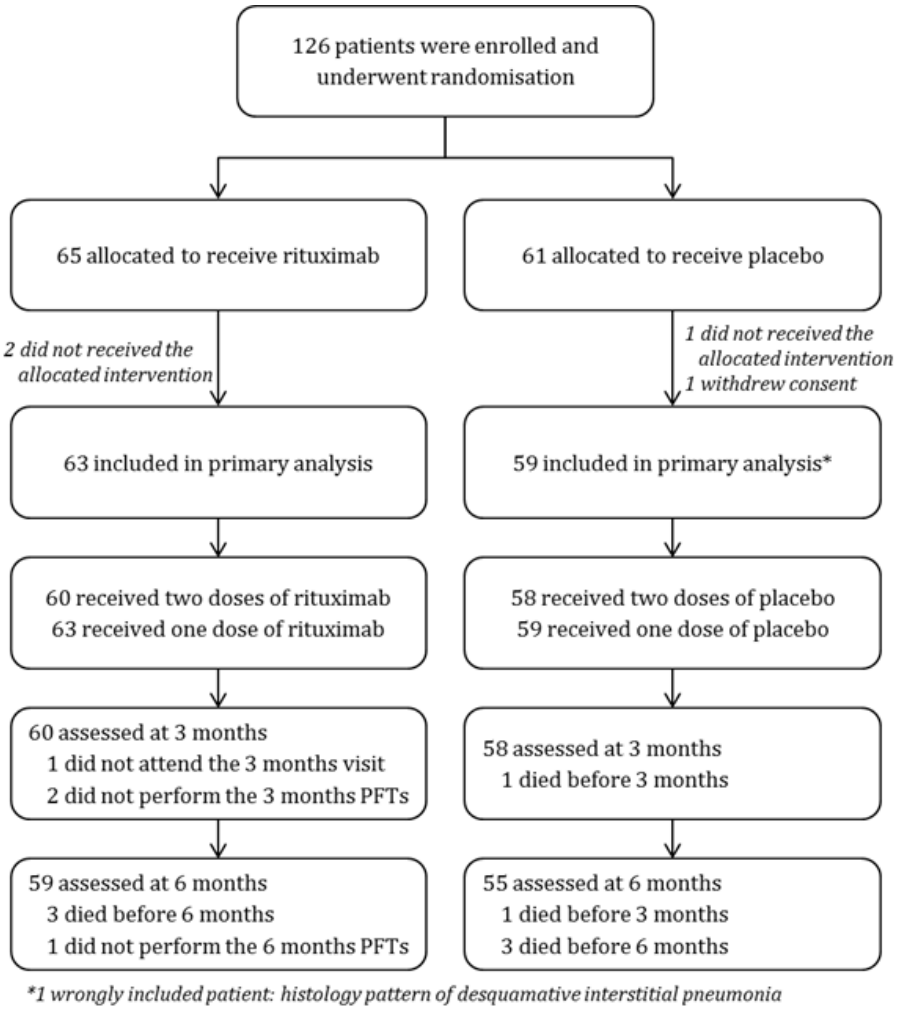

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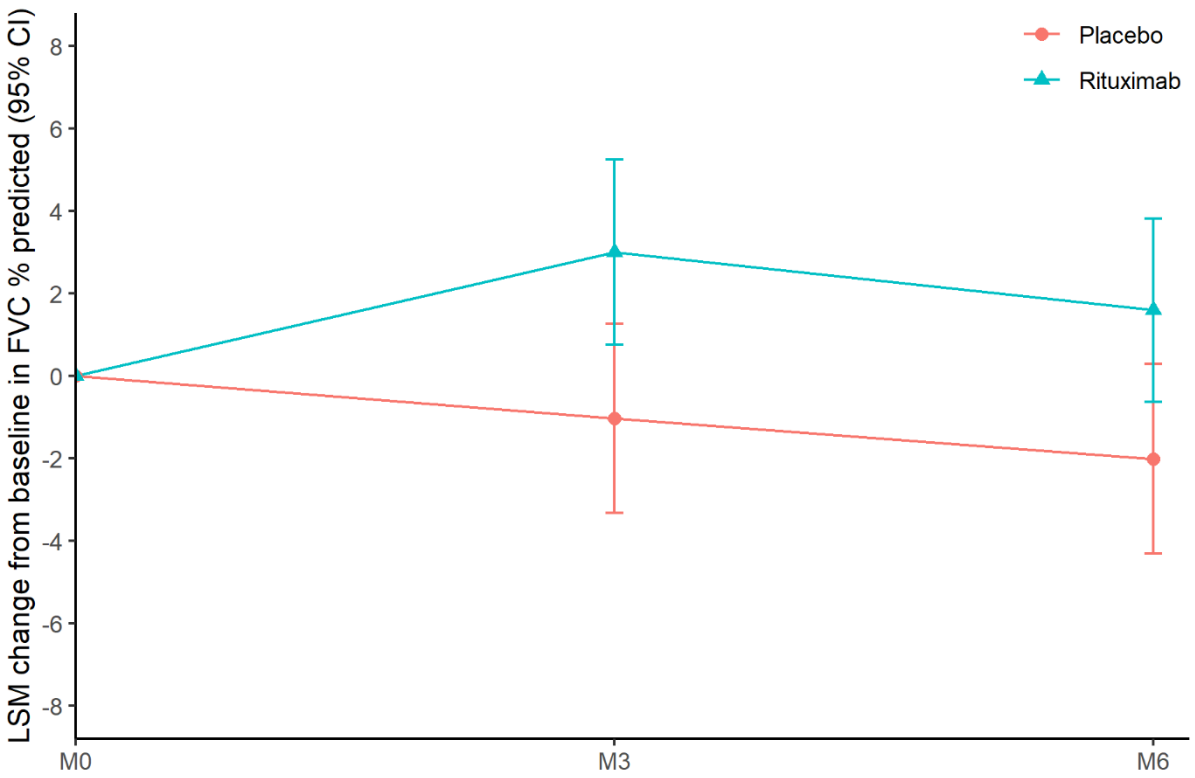

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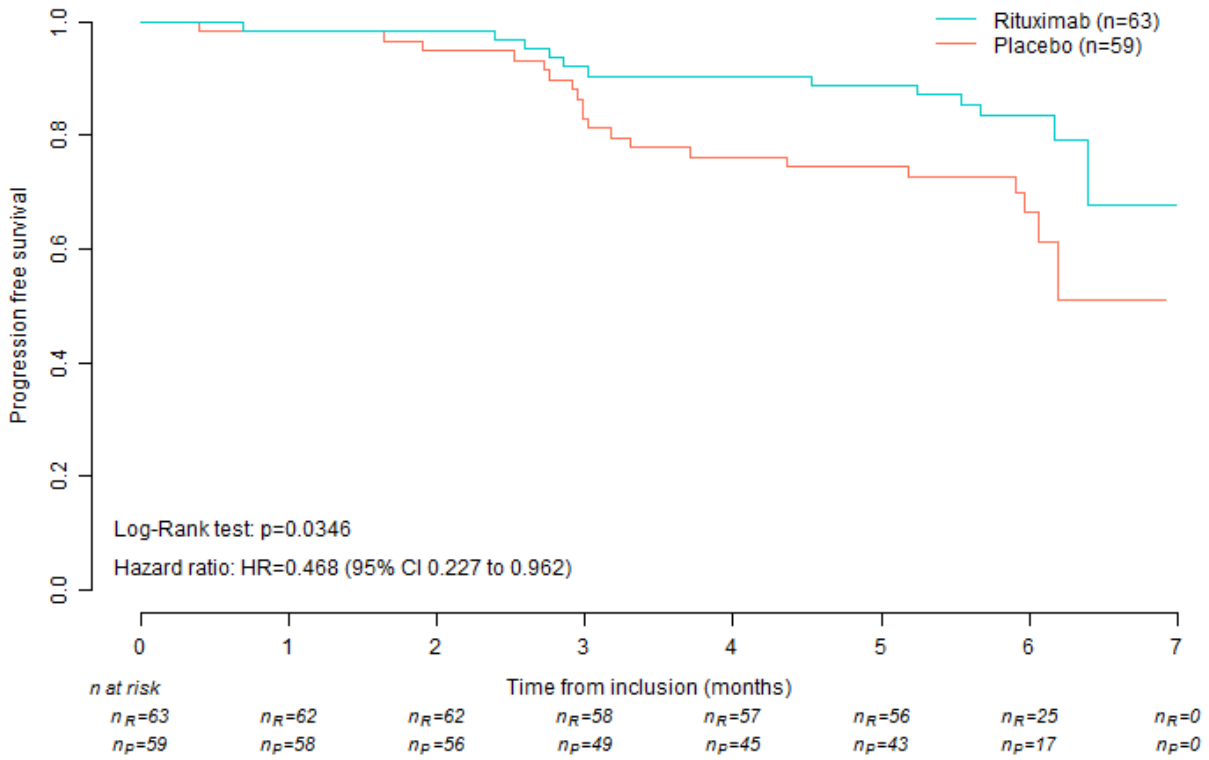
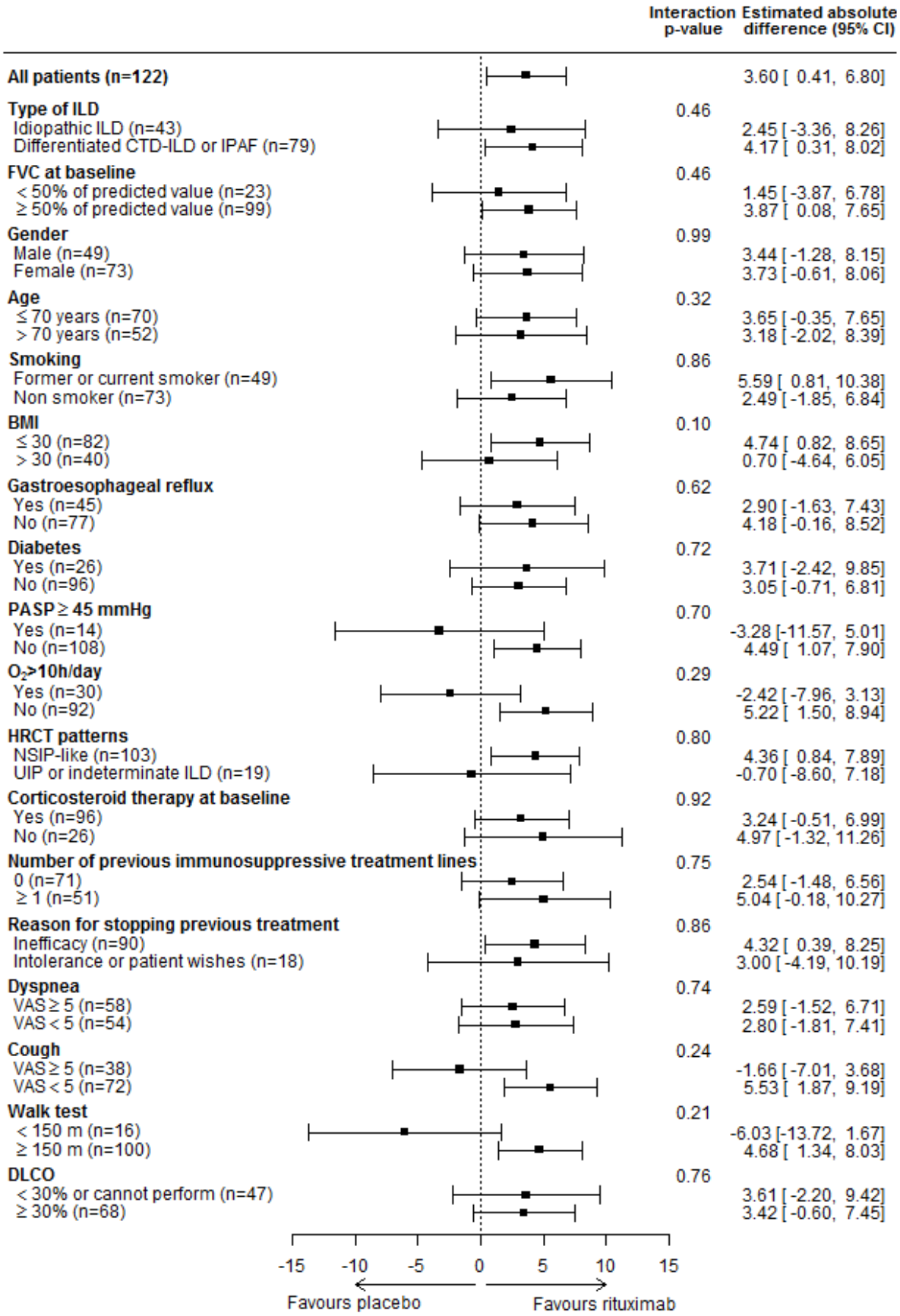


ACCEPTED MANUSCRIPT / CLEAN COPY



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