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Original Research

Patient-reported outcomes in a phase II randomised study of regorafenib compared with lomustine in patients with relapsed glioblastoma (the REGOMA trial)

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KEYWORDS
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Abstract ***Background:*** The REGOMA trial showed that regorafenib significantly improved overall survival in patients with recurrent glioblastoma compared with lomustine. Patients treated with regorafenib experienced a higher occurrence of grade 3–4 drug-related adverse events than those receiving the standard treatment. Because this safety profile was expected, it was considered of great importance to assess the patient point of view regarding the disease and treatment impact on different aspects of life and patient well-being. We here report the final results of the health-related quality of life (HRQoL) assessment, a secondary end-point of the study. This trial is registered with ClinicalTrials.gov, NCT02926222.

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of life;
Randomised phase II trial

Methods: Patient-reported outcomes were assessed, within a prospective, randomised, multicentre, open-label phase II trial, by the European Organisation for Research and Treatment of Cancer core questionnaire and brain module at baseline and every 8-weekly neuroradiological assessment till disease progression. Mixed-effect linear models were fitted for each of the HRQoL domain to examine the change over progression-free time within and between arms. Furthermore, differences were also classified as clinically meaningful changes. To correct for multiple comparisons and avoid type I errors, the level of significance was set at P = 0.01 (2-sided).

Results: Of 119 enrolled patients, 56/59 (95%) patients and 58/60 (97%) patients treated with regorafenib and lomustime completed questionnaires at baseline, respectively. No significant differences were observed in any generic or cancer-specific domain during treatment in both arms, or between the two arms, except for the appetite loss and diarrhoea scales which were significantly worse in patients treated with regorafenib. The rate of patients with a clinically meaningful worsening for appetite loss, diarrhoea and for any other domain was not statistically different between the two arms.

Conclusions: Regorafenib did not negatively affect HRQoL in patients with recurrent glioblastoma. These data combined with the survival benefit shown in the REGOMA trial support the use of regorafenib as a treatment option for these patients.

1. Introduction

Regorafenib is an orally available inhibitor of several kinases involved in tumour angiogenesis (VEGFR1–3 and TIE2), oncogenesis (*KIT, RET, RAF1 and BRAF* genes), the tumour microenvironment (platelet-derived growth factor receptor and fibroblast growth factor receptor) and tumour immunity (colony-stimulating factor 1 receptor). REGOMA, a randomised, multicentre, open-label phase II trial performed in 10 Italian centres, compared the efficacy of regorafenib 160 mg once daily for the first 3 weeks of each 4-week cycle versus lomustine 110 mg/m^2 once every 6 weeks till disease progression, death, unacceptable toxicity or consent withdrawal, in recurrent glioblastoma [1]. The overall survival primary end-point was significantly improved with regorafenib (median: 7.4 months, 95% confidence interval (CI): 5.8 to 12.0) compared with lomustine (median: 5.6 months, 95% CI: 4.7 to 7.3; hazard ratio: 0.5, 95% CI: 0.3 to 0.7; log-rank p = 0.0009). Grade 3–4 treatment-related adverse events occurred in 33 (56%) of 59 patients treated with regorafenib and 24 (40%) of 60 patients treated with lomustine. The most frequent grade 3 or 4 adverse events related to regorafenib than lomustine were a greater incidence of blood bilirubin increase (10% in the regorafenib arm vs 0% in the lomustine arm), lipase increase (10% vs 2%), hand-foot skin reaction (10% vs 0%) and rash or desquamation (3% vs 0%). Conversely, lomustine was associated with a higher rate of grade 3–4 haematological toxicity such as neutropenia (2% in the regorafenib group vs 12% in the lomustine group), decreased platelet count (2% vs 13%) and decreased lymphocyte count (5% vs 13%). No death was considered to be drug-related.

These results showed a substantial and clinically meaningful increased overall survival for patients receiving regorafenib compared with those treated with lomustine. However, the occurrence of grade 3–4 drug-related adverse events in the regorafenib group was higher than those in the lomustine group. Because this safety profile was expected in the REGOMA trial, it was considered of great importance to assess the patient point of view regarding the disease and treatment impact on different aspects of life and patient well-being. On the other hand, in patients with recurrent glioblastoma, treatment options are very limited [2], and any trial showing survival benefit is therefore highly relevant; hence, in the REGOMA trial, the analysis of health-related quality of life (HRQoL) is a crucial point.

Indeed, a planned secondary end-point of this study was the patients' self-assessment of disease symptoms and disease treatment burden and was evaluated comparing patient-reported outcomes (PROs) between the two treatment groups by means of the European Organisation for Research and Treatment of Cancer (EORTC) quality of life instruments.

Here, we report the final PRO analysis from the REGOMA trial.

2. Methods

2.1. Study design and patients

REGOMA, a prospective, randomised, multicentre, open-label phase II trial was conducted in 10 Italian clinical centres (three comprehensive cancer centres, three university hospitals, two neurological hospitals and two general hospitals). Enrolled patients had histologically confirmed glioblastoma with

unequivocal first progression after surgery followed by radiotherapy and temozolomide chemotherapy in accordance with response assessment in neuro-oncology (RANO) criteria. Other major inclusion criteria were age at least 18 years; Eastern Cooperative Oncology Group performance status score of 0–1; adequate bone marrow, liver and renal function. No previous chemotherapy for recurrent disease or previous treatment with regorafenib or any other VEGFR-targeting kinase inhibitor were allowed. All participating centres obtained written approval for the study from their local authorities and ethics committees. All patients signed an informed consent form approved by the ethics committee of the enrolling institution in accordance with national regulations. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Eligible patients were randomly assigned (1:1) to receive either regorafenib or lomustine by a web-based system, stratified in block sizes of four by centre and surgery at recurrence (yes vs no). Neither investigators nor patients were masked to treatment allocation.

2.2. Outcomes

The primary end-point was overall survival, defined as the time from randomisation to death from any cause. Results have been previously published [1].

PROs represented a secondary end-point evaluated by means of (HRQoL) questionnaires without any scales selected *a priori* as of primary interest.

2.3. Treatment

Patients were randomised to receive regorafenib 160 mg (given as four 40 mg tablets) orally once daily for the first 3 weeks of each 4-week cycle or lomustine 110 mg/m^2 (in 40 mg capsules, up to a maximum dose of 200 mg) orally on day 1 of every 6-week cycle till disease progression (as per RANO criteria), death, unacceptable toxicity or consent withdrawal. Further details on treatment management and baseline characteristics of patients have already been reported elsewhere [1].

2.4. PRO measurement

PROs were captured through standardised measures of HRQoL using the Italian version 3.0 of the generic Quality of Life Questionnaire Core 30 [3] (QLQ-C30) and the specific brain module [4] (QLQ-BN20) of the EORTC. Investigational site staff distributed questionnaires to patients, who were solely responsible for self-administering the questionnaires. The HRQoL questionnaires were completed by patients before seeing the physician to avoid potential bias. Questionnaires were administered at baseline and concurrently with magnetic resonance imaging (MRI) assessments, every 8 weeks till disease progression.

The generic EORTC QLQ-C30 includes 30 items that are grouped into five functional scales (physical, role, emotional, cognitive and social), a global health status scale, three symptom scales (fatigue, nausea and vomiting and pain) and six symptom single-item measures (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).

The specific brain cancer EORTC QLQ-BN20 includes 20 items that are grouped into 11 symptom scales/single items (future uncertainty, visual disorder, motor dysfunction, communication deficit, headaches, seizures, drowsiness, itchy skin, hair loss, weakness of legs and bladder control).

For functional scales, as well as for the global health status scale, higher scores represent higher levels of functioning and higher HRQoL. For symptom scales and items, higher scores represent higher levels of symptomatology or problems. Following the scoring manual [5], all scores were linearly transformed to range from 0 to 100.

2.5. Statistical analysis

HRQoL questionnaires were administered at baseline, before randomisation, and at the time of each neuroradiological assessment, before performing the examination, scheduled every 8 weeks (±1 week). HRQoL forms completed at the time of disease progression were excluded. Compliance was calculated as the number of acceptable forms received of the number expected at each assessment point, and differences were tested using the Fisher exact test. The number of expected forms at each assessment point was the number of patients who did not experience disease progression till that time.

As the study was powered to detect differences between arms related to overall survival, no sample size calculation was performed related to HRQoL differences. All analyses were based on the intention-to-treat population (including patients in the group to which they were assigned, whether or not they received the allocated treatment) who completed at least one-time point questionnaire. The per-protocol population coincided with the intention-to-treat population; therefore, analysis on this population was not conducted.

Patient characteristics are described using medians and interquartile ranges for quantitative data and frequencies and percentages for categorical data. HRQoL scores are reported as the mean and standard deviation by the treatment group and assessment time.

The questionnaires were scored in accordance with their standard procedures [5], provided that at least half of the items on the scale had been answered. Mixed-effect linear models were used to examine the changes in each score over time within treatment groups and the differences between the two treatments groups, including the

interaction with time and a compound symmetry covariance matrix for random effects [6]. Kenward-Roger degrees-of-freedom approximation was used to model all available data from each patient. No formal imputation procedure was used. These analyses were restricted to patients who were progression-free at the time of assessment, to evaluate the treatment impact on HRQoL.

To further investigate the detrimental impact of treatments on patients' HRQoL, the proportion of patients who had a clinically meaningful deterioration was also evaluated [7]. A reduction by at least 10 or more points on a functional scale was classified as a clinically meaningful deterioration, whereas an increase by 10 or more points was interpreted as worsening of a given symptom.

To reduce the possibility of false-positive statistical testing, all statistical tests used a two-sided 1% significance level. Differences within and between treatment groups were interpreted also as per their magnitude, with a minimally important difference ranging from 4 to 11 points for the EORTC QLQ-C30 scales [8] and 10 points (on a 0–100 scale) being judged as the threshold for clinically relevant changes for the EORTC QLQ-BN20 scales [9,10].

The steroid dosage, which may be associated with general physical functioning as rated by the treating physician, was recorded at each clinical assessment; the group of patients without steroid treatment at baseline was analysed for the variable 'time to initiation of steroid medication (TISM)'. TISM was estimated using the Kaplan–Meier method, and treatment arms were compared with the log-rank test.

Statistical analyses were performed using the SAS statistical package (SAS, rel. 9.4; SAS Institute Inc.).

The requirements established by EORTC [11] and the CONSORT PRO guidelines [12] for reporting HRQoL in randomised controlled trials were used to report the details in full. The trial was not overseen by a data monitoring committee. It is registered with the EU Clinical Trials Register database, number 2014-003722-41 and with ClinicalTrials.gov, number NCT02926222.

3. Results

Between 27th November 2015 and 23rd February 2017, 119 eligible patients were randomly assigned (59 in the regorafenib group and 60 in lomustine group).

Four patients did not participate in the HRQoL evaluation, two in the regorafenib group and two in the lomustine group, respectively (Fig. 1). One hundred and fourteen patients completed the baseline HRQoL questionnaire, giving a baseline completion rate of 95.8%. Table 1 shows the patterns of available questionnaires. One patient missed the baseline measurement.

The compliance with the completion of the HRQoL questionnaires is displayed in Table 2. There were no statistically significant differences in compliance between the two arms at each time assessment.

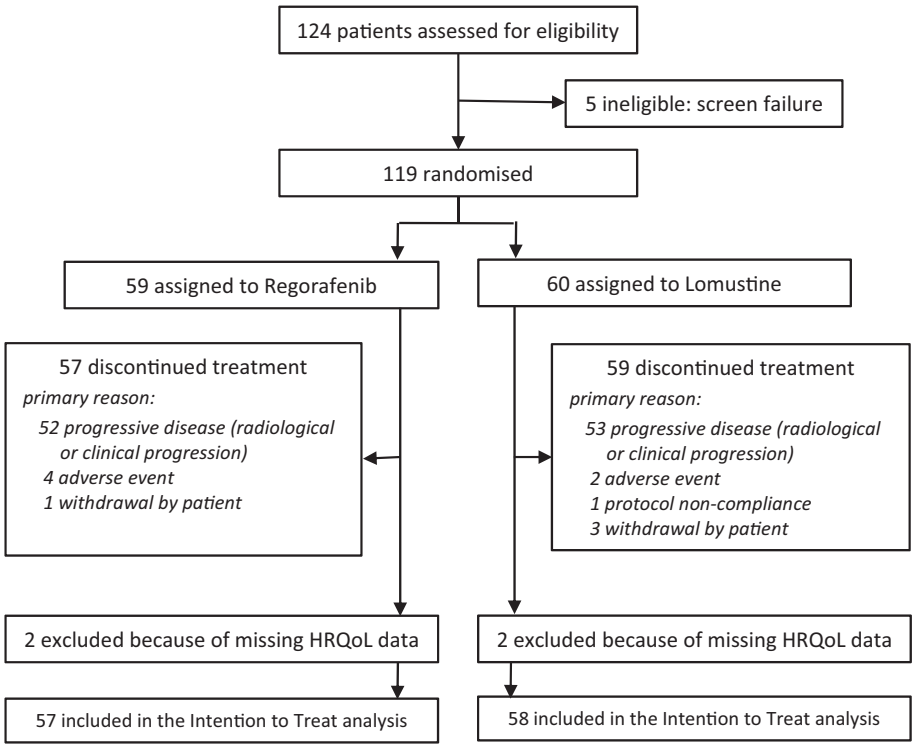

Fig. 1. CONSORT diagram.

Table 1
Pattern of available questionnaires for patients who did not experience disease progression.

Baseline	Week 8	Week 16	Week 24	Week 32	Week 40	Week 48	Week 56	Week 64	Frequency
									4
	×	×	×	×	×	×	×	×	1
×									77
×	×								20
×	×		×	×	×	×	×		1
×	×	×							7
×	×	×			×				1
×	×	×	×						3
×	×	×	×	×			×	×	1
×	×	×	×	×	×				2
×	×	×	×	×	×	×		×	1
×	×	×	×	×	×	×	×		1
114	**38**	**17**	**10**	**7**	**7**	**4**	**4**	**3**	**119**

Table 2
Compliance with completion of questionnaires for each treatment arm.

	Baseline	Week 8	Week 16	Week 24	Week 32	Week 40	Week 48	Week 56	Week 64
Regorafenib									
Received	56	25	14	9	6	5	3	3	3
Expected	59	25	15	11	7	6	5	5	3
% compliance	94.9%	100.0%	93.3%	81.8%	85.7%	83.3%	60.0%	60.0%	100.0%
Lomustine									
Received	58	13	3	1	1	2	1	1	
Expected	60	13	4	3	2	2	1	1	
% compliance	96.7%	100.0%	75.0%	33.3%	50.0%	100.0%	100.0%	100.0%	
P-value	*0.6794*	*1.000*	*0.386*	*0.1758*	*0.4167*	*1.000*	*1.000*	*1.000*	
Overall									
Received	114	38	17	10	7	7	4	4	3
Expected	119	38	19	14	9	8	6	6	3
% compliance	95.8%	100.0%	89.5%	71.4%	77.8%	87.5%	66.7%	66.7%	100.0%

Because of the low number of progression-free patients from week 24 onwards, we did not use these data to perform the comparisons. Globally, 169 (96%) forms of 176 expected were available for the longitudinal analysis.

Baseline characteristics for the 115 patients who completed at least one questionnaire were well-balanced between the two groups (Table 3). Most patients were men (70% and 71%, respectively), and most patients had not undergone surgery at the time of recurrence (79% and 78%, respectively).

Mean observed scores by the treatment group over time are shown in Table 4.

Patients treated with regorafenib had a clinically relevant and statistically significant loss in appetite (Fig. 2; mean difference over all time points between groups: −15.7 points, 95% CI: −27.5 to −4.0) and a clinically relevant and statistically significant worst diarrhoea (Fig. 2; mean difference over all time points between groups: −13.5 points, 95% CI: −22.8 to −4.3). No further statistically significant differences were observed from the longitudinal mixed analyses in any other generic or cancer-specific domains between the two arms.

Overtime (Fig. 3A–C), HRQoL scores did not significantly change across the study period for the lomustine group, whereas appetite loss (8 weeks: 10.6 points, 95% CI: 0.8 to 20.3; 16 weeks: 21.1 points, 95% CI: 8.7 to 33.4) pain (8 weeks: 13.0 points, 95% CI: 4.7 to 21.4; 16 weeks: 13.8 points, 95% CI: 3.3 to 24.3) and

Table 3
Patients' characteristics for each treatment arm.

	Regorafenib group (*N = 57*)	Lomustine group (*N = 58*)
Age (years)	54.8 (46.8–60.9)	58.9 (51.8–66.0)
Sex		
Male	40 (70%)	41 (71%)
Female	17 (30%)	17 (29%)
ECOG performance status		
0	25 (44%)	26 (45%)
1	32 (56%)	32 (55%)
Corticosteroids use	31 (54%)	39 (67%)
Surgery at the time of recurrence	12 (21%)	13 (22%)
MGMT status		
Methylated	29 (51%)	27 (48%)
Unmethylated	28 (49%)	29 (52%)

ECOG, Eastern Cooperative Oncology Group; MGMT, O-6-methylguanine-DNA methyltransferase gene.

diarrhoea (8 weeks: 13.2 points, 95% CI: 5.1 to 21.4; 16 weeks: 21.0 points, 95% CI: 10.8 to 31.3) significantly and clinically increased from baseline for patients treated with regorafenib. Furthermore, a significant treatment effect was observed for the regorafenib group in physical functioning at 16 weeks (−12.6 points, 95% CI: −21.4 to 3.8) that clinically deteriorated, and seizures at 8 weeks (9.9 points, 95% CI: 2.9 to 16.8), however, were not clinically relevant.

A higher proportion of patients in the regorafenib arm reported a clinically meaningful deterioration at first MRI assessment (8 weeks from starting treatment) in the physical (45.8% vs 30.8%), emotional (37.5% vs 23.1%) and social functioning (33.3% vs 23.1%), fatigue (54.2% vs 46.2%), nausea (20.8% vs 7.7%), pain (37.5% vs 30.8%), dyspnoea (16.7% vs 7.7%), insomnia (33.3% vs 23.1%), appetite loss (29.2% vs 0%), constipation (29.2% vs 23.1%), diarrhoea (37.5% vs 7.7%), future uncertainty (29.2% vs 23.1%), communication deficit (33.3% vs 23.1%), headaches (25.0% vs 7.7%), seizures (20.8% vs 0%), itchy skin (16.7% vs 0%), hair loss (20.8% vs 0%) and bladder control (25.0% vs 7.7%) compared with patients in the lomustine arm (see Fig. 4). Although, the patients treated with regorafenib highlighted a trend for a clinically meaningful deterioration for those items compared with the patients receiving lomustine, none of these differences were statistically significant.

Regarding steroid administration, 50 patients did not take dexamethasone at baseline; among these, subsequently, 24 patients received dexamethasone during the antineoplastic treatment: 14 in the regorafenib arm and 10 in the lomustine arm. The median TISM was not statistically different between the two arms: 3.1 months (95% CI: 0.7 to not estimable, NE) and 3.0 (95% CI: 0.7 to NE) in the regorafenib group and lomustine group (log-rank p = 0.6499), respectively.

4. Discussion

In this pre-specified secondary end-point analysis of the REGOMA study, we investigated PROs assessed

Table 4
Mean scores and standard deviations (SDs) for all domains of the EORTC QLQ-C30 and QLQ-BN20 questionnaires.

Mean (SD)	T0		T1		T2	
	Baseline		Week 8		Week 16	
	Regorafenib	Lomustine	Regorafenib	Lomustine	Regorafenib	Lomustine
Global health status[a]	63 (21)	61 (21)	61 (20)	58 (17)	54 (23)	47 (32)
C30 functional scales[a]						
Physical functioning	79 (22)	75 (25)	77 (21)	67 (29)	71 (26)	67 (23)
Role functioning	73 (30)	72 (31)	71 (29)	55 (27)	63 (34)	67 (33)
Emotional functioning	74 (23)	77 (18)	72 (25)	78 (15)	77 (16)	72 (10)
Cognitive functioning	78 (26)	69 (28)	81 (26)	67 (30)	75 (21)	83 (29)
Social functioning	79 (26)	73 (29)	76 (25)	83 (25)	76 (29)	72 (35)
C30 symptom scales[b]						
Fatigue	30 (22)	34 (24)	38 (27)	40 (30)	41 (29)	30 (6)
Nausea/vomiting	2 (7)	4 (9)	9 (20)	1 (5)	4 (7)	6 (10)
Pain	8 (16)	7 (13)	21 (30)	14 (20)	24 (32)	6 (10)
Dyspnoea	5 (18)	8 (18)	9 (20)	3 (9)	12 (28)	11 (19)
Insomnia	15 (24)	20 (27)	21 (32)	15 (22)	31 (38)	0 (0)
Appetite loss	9 (20)	9 (17)	19 (32)	3 (9)	31 (44)	0 (0)
Constipation	10 (21)	12 (21)	16 (26)	18 (22)	19 (34)	0 (0)
Diarrhoea	4 (13)	2 (11)	17 (29)	3 (9)	26 (37)	0 (0)
Financial difficulties	18 (27)	18 (29)	12 (19)	21 (26)	24 (30)	11 (19)
BN20 symptom scales[b]						
Future uncertainty	33 (27)	40 (23)	29 (25)	34 (17)	29 (20)	25 (22)
Visual disorder	17 (23)	13 (19)	13 (22)	14 (17)	14 (17)	11 (11)
Motor dysfunction	17 (21)	23 (25)	18 (24)	39 (37)	20 (29)	26 (23)
Communication deficit	20 (28)	25 (29)	18 (29)	23 (34)	23 (32)	22 (38)
Headaches	12 (21)	10 (18)	17 (32)	3 (9)	17 (31)	11 (19)
Seizures	2 (14)	4 (11)	12 (27)	0 (0)	5 (12)	0 (0)
Drowsiness	30 (26)	34 (28)	24 (21)	38 (27)	38 (37)	33 (0)
Itchy skin	8 (16)	10 (18)	14 (24)	3 (9)	17 (36)	0 (0)
Hair loss	15 (29)	11 (22)	17 (30)	0 (0)	14 (31)	0 (0)
Weakness of legs	22 (26)	22 (29)	25 (31)	38 (43)	26 (28)	11 (19)
Bladder control	8 (20)	14 (24)	16 (31)	18 (32)	12 (28)	11 (19)
# of patients	**56**	**58**	**25**	**13**	**14**	**3**

EORTC, European Organisation for Research and Treatment of Cancer; QLQ-BN20, Quality of Life Questionnaire brain cancer module; QLQ-C30 Quality of Life Questionnaire Core 30; SD, standard deviation

[a] Higher scores represent a higher level of functioning.

[b] Higher scores represent a higher level of symptomatology.

through HRQoL which are crucial to estimate the real impact of treatments from the patient's point of view.

The REGOMA trial demonstrated promising activity of regorafenib in patients with recurrent glioblastoma. However, compared with lomustine, regorafenib showed a greater incidence of certain grade 3–4 adverse events. Despite these differences in adverse events, the current longitudinal analysis of PROs demonstrated that HRQoL and functioning were maintained in both groups. A relevant and statistically significant difference was only observed in appetite loss and diarrhoea that significantly increased during the treatment in patients receiving regorafenib; nevertheless, it was consistent with the adverse event profile of this drug. A small deterioration from baseline was also observed for physical function, pain and seizure in the regorafenib arm at 16, 8 and 8 weeks, respectively.

At 8 weeks, more patients treated with regorafenib reported a clinically meaningful deterioration in many items compared with patients receiving lomustine. Although none of these differences was statistically significant, it needs to be noted the results could be affected by the small sample size, dropout over time and the fact that the study was not powered to HRQoL outcomes.

Steroid-related adverse events could significantly affect QoL in patients with glioma; in our study, the rate of patients taking steroids at baseline was higher in the lomustine group (62% vs 53% in the regorafenib arm), but the median TISM was similar between the two arms; these characteristics could demonstrate that steroids had a minimal impact on HRQoL, regardless of the cancer treatment received. Indeed, a similar finding was observed in patients with recurrent glioblastoma treated

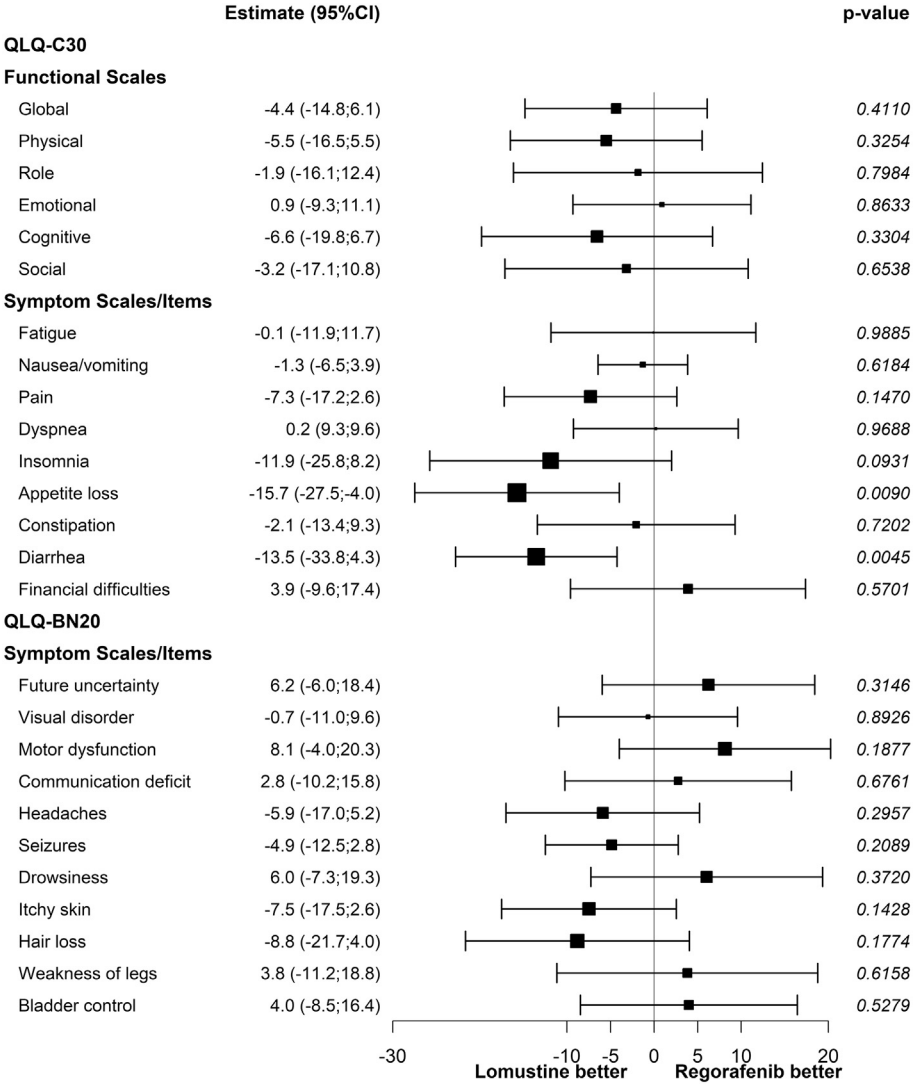

Fig. 2. Forest plot of estimated differences (regorafenib and lomustine) over all time points (repeated-measure mixed-effect models) in the PRO-evaluable population for the preselected items/scales. The box size is proportional to the estimated effect of each scale. P values are not adjusted for multiplicity. EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; QLQ-BN20, Quality of Life Questionnaire brain cancer module; QLQ-C30, Quality of Life Questionnaire Core 30.

with lomustine plus bevacizumab compared with lomustine alone (EORTC 26101) [13], where no significant difference in the time before starting steroids was shown between the combination regimen and the monotherapy group. The impact of bevacizumab on HRQoL was also analysed in this phase III clinical trial without reporting significant between-group differences for preselected scales and no significant differences in the mean change in HRQoL from baseline at weeks 12 and 24 between the groups. Conversely, the two randomised phase III studies analysing bevacizumab in association with radiochemotherapy in newly diagnosed patients with glioblastoma (AVAglio [14] and RTOG 0825 [15] studies) reported conflicting results in interpretation of HRQoL.

Various studies analysing regorafenib in other types of cancers, such as advanced gastric adenocarcinoma and soft-tissue sarcoma, showed that this treatment does not impact HRQoL [16,17]. Noteworthy, HRQoL data were pooled across four trials studying regorafenib in patients with metastatic colorectal cancer (CORRECT and CONCUR trials), GIST (GRID trial) and hepatocellular carcinoma (RESORCE): this analysis showed that HRQoL is maintained in these patients without significant differences compared with placebo [18]. These results are in line with our data in patients with recurrent glioblastoma. Notably, we excluded questionnaires assessed at the time of progression because glioblastoma growth can affect HRQoL itself [19,20]. Other strengths of our analysis include the fact that the compliance was very high with excellent completion rates (96% at baseline and 100% at week 8) and was well-balanced between the two groups. Moreover, all the questionnaires were administered before the patients were informed of the neuroradiological response to avoid any influence on the HRQoL scores. In addition, the PRO evaluation was a secondary end-point of the REGOMA trial, and the EORTC QLQ-C30 and EORTC BN-20 are the most used and validated questionnaires to relevant clinical changes in HRQoL for patients with glioma [21]. Furthermore, analysing data to highlight clinical meaningful differences at the individual level and evaluating mean changes for all patients together, our study showed that consistent conclusions about the impact of treatments on patient HRQoL were obtained [7].

However, our study has some limitations. First, REGOMA is a relatively small, open-label phase II trial

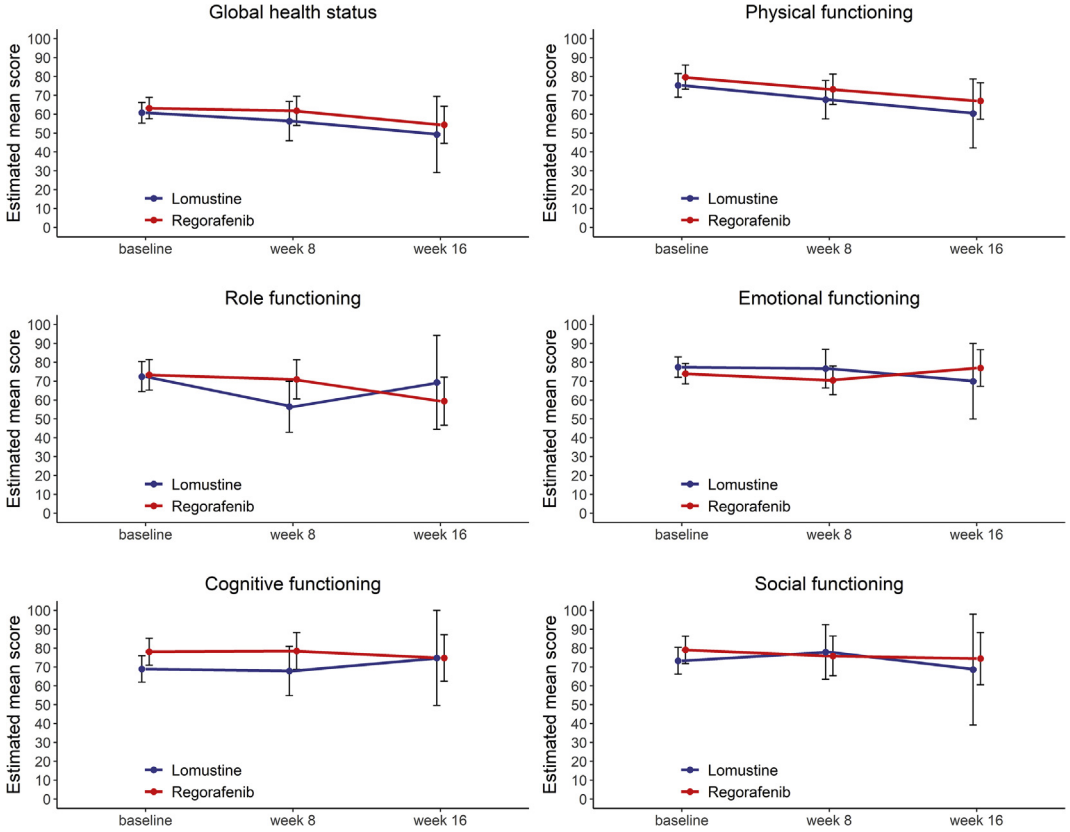

Fig. 3A. Health-related Quality of Life (HRQoL) scores over time for the EORTC QLQ-C30 functional scales in PRO-evaluable population. Data are presented as estimated mean HRQoL scores (repeated-measure mixed-effect models) at every time point, together with their 95% confidence interval. A higher score represents a higher level of functioning. EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; QLQ-C30, Quality of Life Questionnaire Core 30.

and was not powered to reveal significant or clinically relevant differences on HRQoL between the patients who received regorafenib and those who received lomustine; second, owing to the short progression free survival (PFS) found in the REGOMA trial and the subsequent limited number of patients assessable for the QoL, the 'clinically meaningful deterioration' was analysed till week 8 (at week 16, we had 15 and 4 patients free of progression in the regorafenib arm and lomustine arm, respectively); thus, it was not possible to evaluate the clinical impact of long-term therapy on HRQoL; noteworthy, patient compliance at week 16 was still high (93% in the regorafenib arm and 75% in the lomustine arm). However, the longitudinal analysis of PROs was performed till week 16

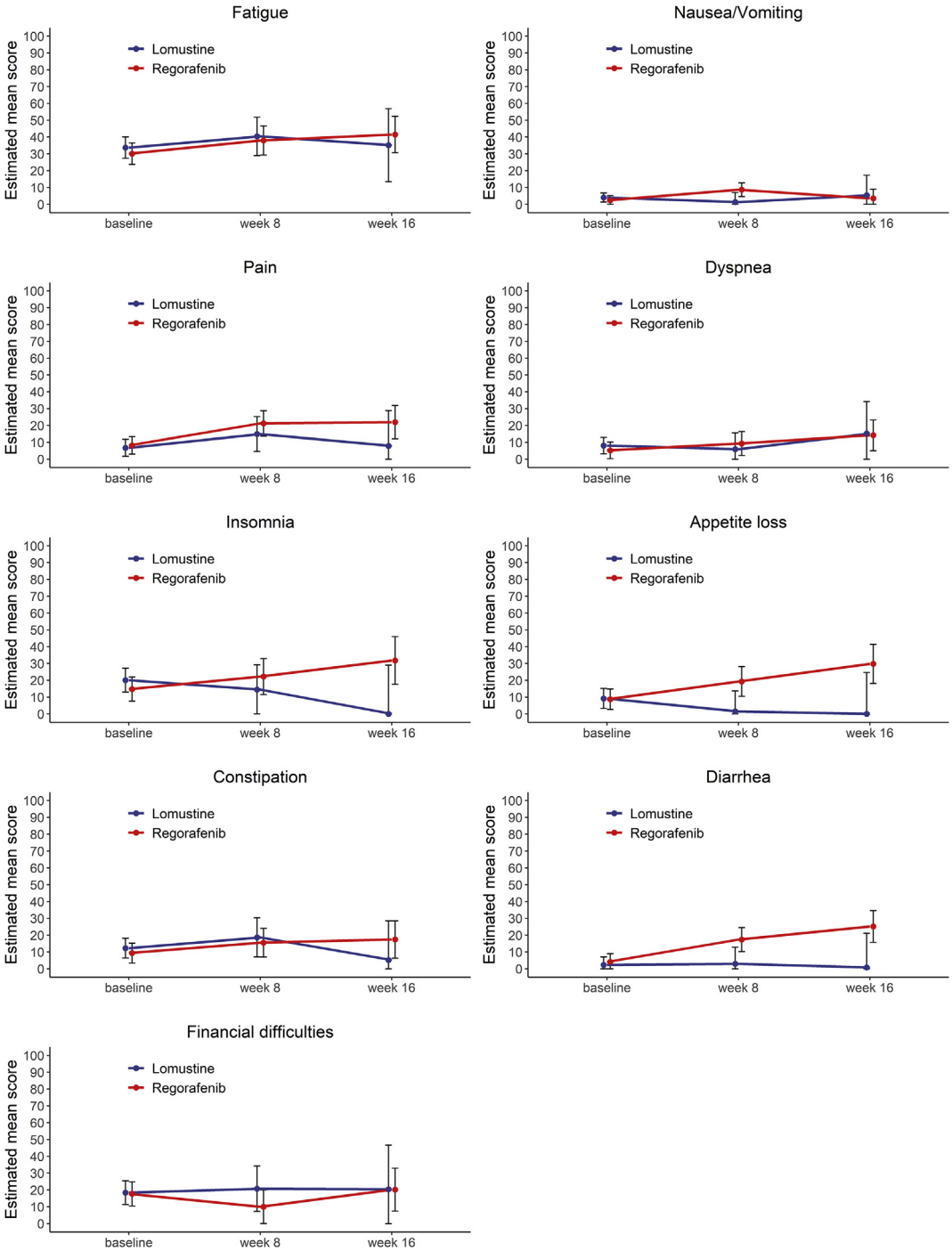

Fig. 3B. Health-related Quality of Life (HRQoL) scores over time for the preselected EORTC QLQ-C30 symptom items/scales in the PRO-evaluable population. Data are presented as estimated mean HRQoL scores (repeated-measure mixed-effect models) at every time point, together with their 95% confidence interval. A higher score represents a higher level of symptoms. EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; QLQ-C30, Quality of Life Questionnaire Core 30.

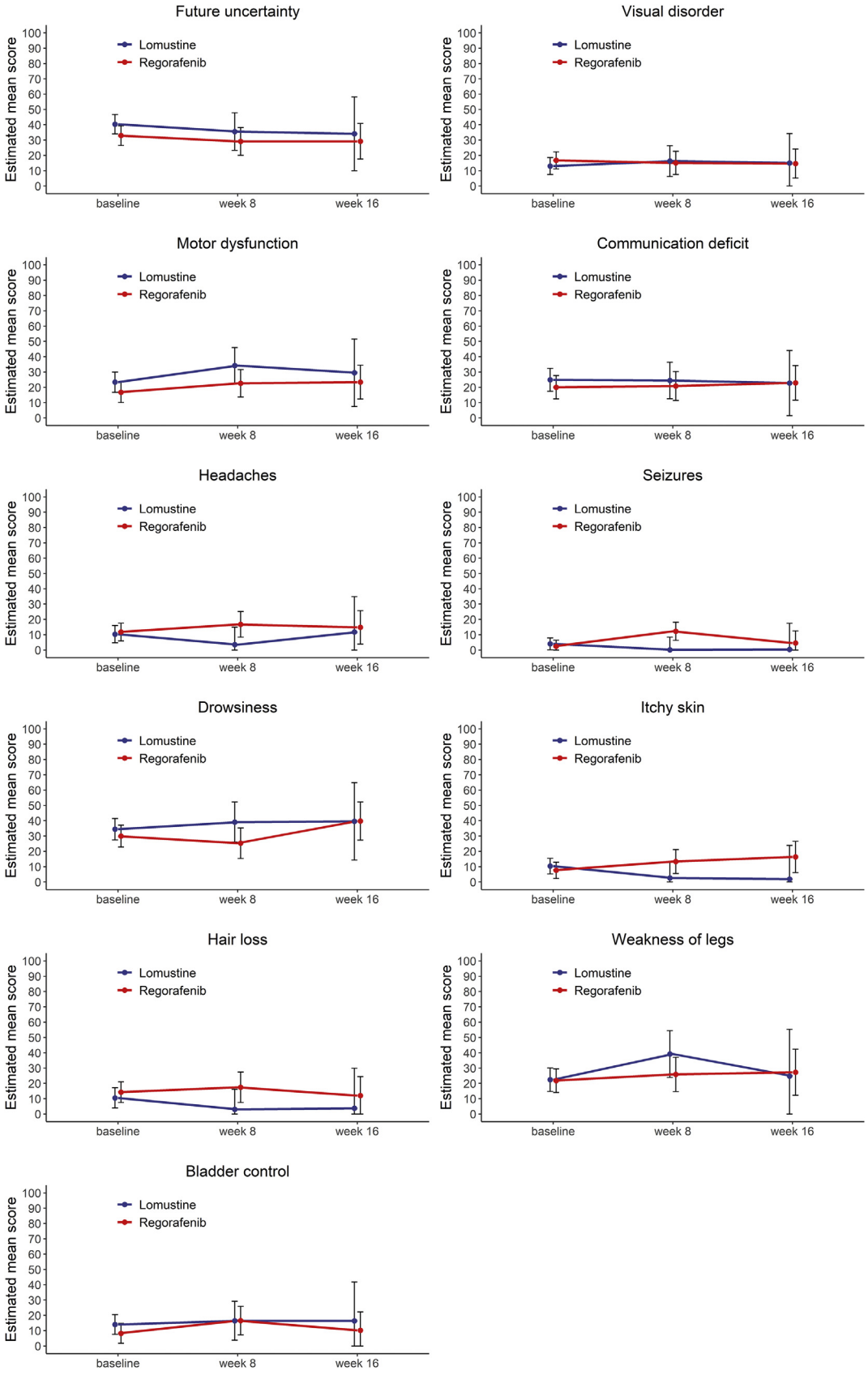

Fig. 3C. Health-related Quality of Life (HRQoL) scores over time for the EORTC QLQ-BN20 symptom items/scales in the PRO-evaluable population. Data are presented as estimated mean HRQoL scores (repeated-measure mixed-effect models) at every time point, together with their 95% confidence interval. A higher score represents a higher level of symptoms. EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; QLQ-BN20, Quality of Life Questionnaire brain cancer module.

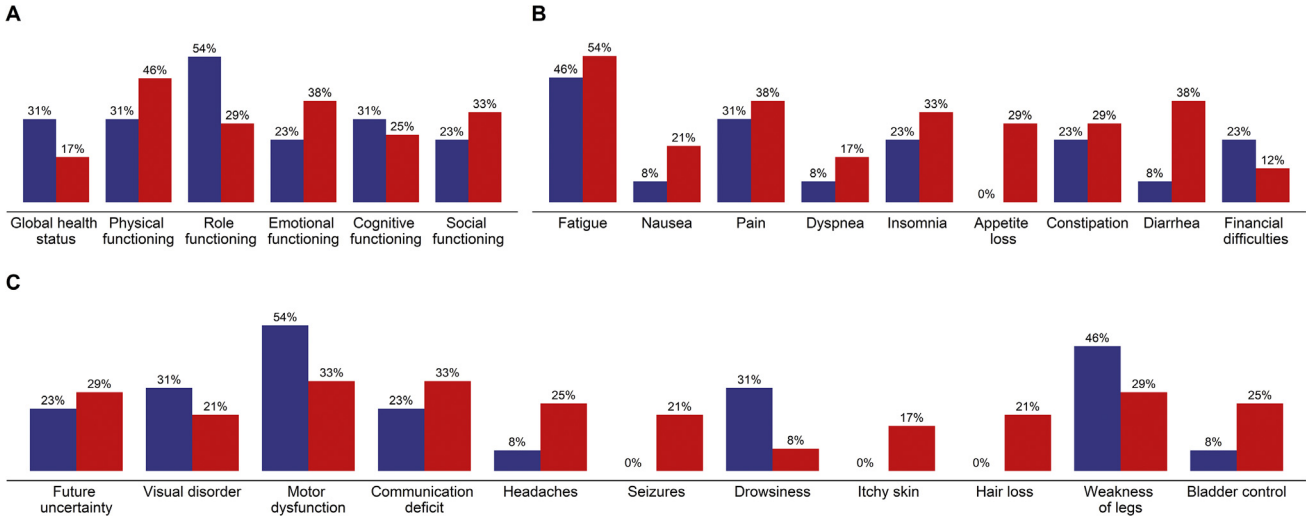

Fig. 4. Proportion of patients experiencing a clinically meaningful deterioration at first magnetic resonance imaging (MRI) assessment in the EORTC QLQ-C30 functional scales (A), symptom items/scales (B)EORTC QLQ-BN20 symptom scales and (C) in the Regorafenib (red colour) and Lomustine (blue colour) PRO-evaluable population. EORTC, European Organization for Research and Treatment of Cancer; PRO, patient-reported outcome; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-BN20, Quality of Life Questionnaire brain cancer module. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(about 4 months from starting the treatment), a longer time than the median duration of second-line treatments in patients with recurrent glioblastoma. Third, because measures of neurocognitive functioning are lacking, we cannot determine the net clinical effect of the treatment.

In conclusion, the REGOMA trial demonstrated that regorafenib did not negatively affect HRQoL in patients with recurrent glioblastoma which reported stable HRQoL and high levels of functioning. Adverse events associated with regorafenib did not appear to have an impact on PROs. These data together with the superior efficacy of regorafenib compared with lomustine from the REGOMA study support regorafenib as the treatment option of choice in this setting of patients.

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Author contribution

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Giovanna Magni: Formal analysis

Gian Luca De Salvo: Conceptualization, Writing - Original Draft

Vittorina Zagonel: Conceptualization, Writing - Review & Editing, Supervision

Conflict of interest statement

GL has declared a consulting or advisory role for funding from Bayer, AbbVie, Orbus Therapeutics and BrainFarm; travel funding from Roche and Bayer; **RR** has declared research funding from Mundipharma, Novocure, UCB; **BD** has declared personal fees from EISAI, ELI LILLY, ASTRA ZENECA, MSD, ROCHE, AMGEN, personal grants and non-financial support from IPSEN, SANOFI and BAYER; **VZ** has declared consulting or advisory role funding from Bristol-Myers Squibb and Merck, Speakers Bureau funding from Bayer, Roche, Bristol-Myers Squibb, Astellas Pharma, Servier, AstraZeneca and Lilly, travel and accommodation funding from Bayer, Roche and Servier.

All remaining authors have declared no conflict of interest to declare.

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