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ORIGINAL RESEARCH

REGOMA-OSS: a large, Italian, multicenter, prospective, observational study evaluating the efficacy and safety of regorafenib in patients with recurrent glioblastoma

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Background: In the randomized phase II REGOMA trial, regorafenib showed promising activity in patients with recurrent glioblastoma. We conducted a large, multicenter, prospective, observational study to confirm the REGOMA data in a real-world setting.

Patients and methods: The major inclusion criteria were histologically confirmed diagnosis of glioblastoma according to the World Health Organization (WHO) 2016 classification and relapse after radiotherapy with concurrent/adjuvant temozolomide treatment, good performance status [Eastern Cooperative Oncology Group performance status (ECOG PS 0-1)] and good liver function. Regorafenib was administered at the standard dose of 160 mg/day for 3 weeks on/1 week off. Brain magnetic resonance imaging was carried out within 14 days before starting regorafenib and every 8-12 weeks. The primary endpoint was overall survival (OS). The secondary endpoints were progression-free survival (PFS), objective response rate, disease control rate (DCR), safety and health-related quality of life. The Response Assessment in Neuro-Oncology (RANO) criteria were used for response evaluation and Common Terminology Criteria for Adverse Events (CTCAE) version 5 for assessment of adverse events (AEs).

Results: From September 2020 to October 2022, 190 patients with recurrent glioblastoma were enrolled from 30 cancer centers in Italy: their median age was 58.5 years [interquartile range (IQR) 53-67 years], 68% were male and 85 (44.7%) were in optimal clinical condition (ECOG PS 0). The number of patients taking steroids at baseline was 113 (60%); the second surgery was carried out in 39 (20.5%). O^6-methylguanine-DNA methyltransferase (MGMT) was methylated in 80 patients (50.3%) and 147 (92.4%) of the patients analyzed had isocitrate dehydrogenase (IDH) wild type. The median follow-up period was 20 months (IQR 15.6-25.5 months). The median OS was 7.9 months ([95% confidence interval (CI) 6.5-9.2 months] and the median PFS was 2.6 months (95% CI 2.3-2.9 months). Radiological response was partial response and stable disease in 13 (7.3%) and 26 (14.6%) patients, respectively, with a DCR of 21.9%. The median number of regorafenib cycles per patient was 3 (IQR 2.0-4.0). Grade 3-4

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drug-related adverse events were reported in 22.6% of patients. A dose reduction due to AEs was required in 36% of patients. No deaths were considered as treatment-related AEs.
Conclusions: This large, real-world observational study showed similar OS with better tolerability of regorafenib in patients with relapsed glioblastoma compared with the REGOMA study.
Key words: glioblastoma, regorafenib, recurrent, REGOMA, real-world

INTRODUCTION

Glioblastoma represents the most frequent malignant tumor of the central nervous system in adults, with poor prognosis and limited therapeutic alternatives.[1] The standard treatment for newly diagnosed glioblastoma remains the most extensive and safe surgical resection followed by radiotherapy with concurrent and adjuvant temozolomide.[2] Inevitably, in almost all patients, and despite this approach, the tumor recurs with survival rates that remain lower than 24 months.[2,3] At recurrence, resurgery and reradiotherapy can be considered in eligible cases but systemic treatment remains the most used approach. Nitrosourea-based regimens and temozolomide rechallenge can be an option, always evaluating the possibility of enrollment in clinical trials.[3] Regorafenib is currently used in several types of solid tumors including colorectal cancer,[4] hepatocarcinoma[5] and gastrointestinal stromal tumors gastrointestinal stromal tumor.[6] Regarding the activity of regorafenib in glioblastoma, a study by Wilhelm et al.[7] showed that the administration of the drug at a dosage of 10 mg/kg determined the reduction of extravasation of gadolinium in glioblastomas induced in rats, significantly correlating with good antitumor activity. In January 2019, Lombardi et al.[8] published the results of the randomized phase II REGOMA trial evaluating the use of regorafenib, an oral inhibitor of multiple kinases involved in tumor growth, in patients with recurrent glioblastoma. In this Italian multicenter study, 119 patients were randomized 1 : 1 to receive regorafenib or lomustine. Regorafenib showed a significant improvement in overall survival (OS) compared with lomustine [7.4 months versus 5.6 months, hazard ratio (HR) 0.50, 95% confidence interval (CI) 0.33-0.75; $P = 0.0009$] with a 12-month OS of 38.9% and 15.0% in the regorafenib and lomustine arm, respectively. The safety profile of regorafenib was consistent with data in the literature, with grade 3-4 adverse events occurring in 56% of treated patients, most commonly hand–foot skin reaction, increased blood bilirubin and increased lipase. There were no treatment-related deaths. Based on these data, the Italian Medicines Agency (AIFA) included regorafenib in the list of drugs that are fully reimbursed by the National Health System (Law 648/1996).[9] To evaluate the efficacy and safety of regorafenib in patients with recurrent glioblastoma and to compare them with the REGOMA results, we designed this study.

PATIENTS AND METHODS

REGOMA-OSS is a prospective, observational, multicenter study involving 30 Italian oncology centers. Inclusion and exclusion criteria were similar to the AIFA recommendations for the use of regorafenib in patients with recurrent glioblastoma and to the REGOMA trial (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.102943). The major inclusion criteria were patients with a confirmed histological diagnosis of glioblastoma [according to the World Health Organization (WHO) 2016 classification] with disease progression/recurrence after radiochemotherapy [according to Response Assessment in Neuro-Oncology (RANO) criteria]; age $\geq$18 years; good general clinical status [Eastern Cooperative Oncology Group performance status (ECOG PS 0-1)] and adequate bone marrow, renal, liver and pancreatic function. Patients who underwent surgery for recurrence were considered eligible for enrollment if the diagnosis of glioblastoma was confirmed on histological examination (no residual disease required for inclusion). The major exclusion criteria for the study were prior chemotherapy treatment for recurrent disease and prior treatment with any vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) inhibitor. All enrolled patients signed an informed consent form as the first procedure of the study. All participating centers obtained approval from their local ethics committee and the study was conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. The starting dose of regorafenib was 160 mg/day for 3 consecutive weeks with 1 week off. Patients continued study treatment until disease progression, unacceptable toxicity, or withdrawal from treatment. At the discretion of the investigator, the dose of regorafenib may be reduced, interrupted or discontinued permanently based on the occurrence of adverse events.[10] A proposal for dose modifications and temporary or definitive discontinuation was described in the protocol (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2024.102943). The clinical and laboratory evaluations during treatment were carried out according to the clinical practice and protocol recommendations (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.102943). The methylation status of the O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter and the isocitrate dehydrogenase (*IDH*) mutational status were assessed locally when available. Treatment efficacy was evaluated locally by gadolinium brain magnetic resonance imaging every 8-12 weeks or as clinically indicated using the RANO criteria. All adverse events, classified according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0,[10] occurring during study treatment and up to 30 days from the last administration of regorafenib were recorded. Health-related quality of life was assessed using the EORTC QLQ C30[11] and QLQ-BN20[12] quality of life questionnaires at baseline and concurrent with magnetic resonance imaging.

Statistical analyses

The primary endpoint was OS, calculated as the time from enrollment to death from any cause or last follow-up. The REGOMA study[8] reported a 1-year survival (95% CI) of 38.9% (26.6% to 51.0%) in patients treated with regorafenib. Using this estimate, with a minimum of 150 patients it is possible to estimate 1-year survival with an accuracy of 7.8% and a 95% CI. Data were analyzed based on the intention-to-treat principle. Secondary endpoints were (i) progression-free survival (PFS), calculated as the time from enrollment to the date of disease progression, assessed according to the RANO criteria, or death, whichever occurs first; (ii) the objective response rate (ORR), defined as the percentage of patients with complete response (CR) and partial response (PR) according to the RANO criteria; (iii) the disease control rate (DCR), defined as the percentage of patients with CR + PR + stable disease (SD); (iv) safety and (v) health-related quality of life. Quantitative variables were described by mean and standard deviation for normally distributed variables, and median and interquartile range (IQR) for skewed distributions; categorical variables were described with frequencies and percentages. Survival times were calculated by the Kaplan–Meier method and summarized using medians and 95% CI and the percentage of patients (95% CI) surviving to 1 year. Multivariate analysis was conducted using the Cox proportional hazards regression method to determine the independent prognostic significance of the clinical factors considered on OS and PFS. A backward variable selection procedure was applied to the covariates with a *P* value of at least 0.2 at univariate analysis. The ORR and DCR were summarized with a binomial 95% exact CI using the Clopper–Pearson method. Treatment toxicity was described in terms of maximum grade per patient by type of adverse event based on the CTAE version 5.0 criteria.[10] Serious adverse events (SAEs) were defined as any medical condition that can lead to death, is life-threatening, or requires inpatient hospitalization or prolongation of an existing hospitalization. Statistical analyses were carried out with SAS (version 9.4; IBM, New York, NY). A *P* value of <0.05 was considered significant.

RESULTS

From September 2020 to October 2022, 190 patients with recurrent glioblastoma were enrolled from 30 Italian cancer centers. Their median age was 58.5 years (IQR 53-67 years); 129 patients (58%) were male and 85 (44.7%) had an optimal clinical status (ECOG PS 0). In the overall study population, 113 patients (59.5%) were taking corticosteroids at the start of regorafenib treatment. Of the 159 patients analyzed, 80 (50.3%) had methylated MGMT promoter status. The IDH mutational status was analyzed in 167 patients and 147 (92.4%) were identified as IDH wild type. Among all enrolled patients, 39 (20.5%) underwent a second surgery at the time of first progression/relapse. Patients' characteristics are listed in Table 1.

Table 1. Patients characteristics

Patients characteristics	Values, *n* (%)
Patients, *N*	190
Age (years), median (IQR)	58.5 (53-67)
Sex, *n* (%)	
Male	129 (68)
Female	61 (32)
ECOG PS, *n* (%)	
0	85 (44.7)
1	105 (55.3)
Corticosteroids, *n* (%)	
Yes	113 (59.5)
No	77 (40.5)
Second surgery, *n* (%)	39 (20.5)
MGMT, *n* (%)	
Methylated	80 (50.3)
Unmethylated	79 (49.7)
Missing	31
IDH, *n* (%)	
Mutated	12 (7.5)
Wild-type	147 (92.4)
Missing	31

ECOG PS, Eastern Cooperative Oncology Group performance status; IDH, isocitrate dehydrogenase; IQR, interquartile range; MGMT, O^6-methylguanine-DNA methyltransferase.

The median number of regorafenib cycles was 3 (IQR 2-4 cycles) with a median treatment duration (including time off the drug and temporary discontinuation) of 10.9 weeks (IQR 7-16.7 weeks). The mean daily dose of regorafenib was 160 mg in 102 patients (53.7%) and <160 mg in 88 patients (46.3%). At the time of the analyses, the median follow-up was 20 months (95% CI 15.6-25.5 months) and 150/190 (78.9%) patients had died. The median OS was 7.9 months (95% CI 6.5-9.2 months) with a 12-month OS rate of 32.2% (95% CI 25.4% to 39.3%). At the analysis cut-off date, 180 (94.7%) patients had disease progression during regorafenib treatment. The median PFS was 2.6 months (95% CI 2.3-2.8 months); the 6-month PFS rate was 13.4% (95% CI 8.9% to 18.7%). Kaplan–Meier plots for OS and PFS are reported in Figure 1.

On multivariate analysis, the prognostic factors identified for OS were ECOG PS (HR 1.5, 95% CI 1.0-2.1) and MGMT methylation status (HR 1.6, 95% CI 1.1-2.3). No clinical factors were significantly associated with PFS in either univariate or multivariate analysis (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.102943). At the time of analysis, 178 (93.7%) patients were evaluable for response: 13 (7.3%) had a PR, while no patients reported a CR, resulting in the ORR of 7.3% (95% CI 4.0% to 12.2%); 26 (14.6%) achieved SD as the best response to treatment. The DCR in the analyzed population was 21.9% (95% CI 16.1% to 28.7%). Response to regorafenib according to RANO criteria is reported in Table 2.

Among patients taking steroids at baseline, 6.5% reduced their steroid dose during regorafenib treatment; among patients with ECOG PS 1 at baseline, 10.8% improved to ECOG PS 0.

In our analysis, we also included 12 patients with IDH-mutant glioblastoma; the median PFS and OS were not statistically different from patients with IDH wild-type glioblastoma; in fact, PFS was very similar in both groups [2.4 months versus 2.3 months in patients with IDH wild type and IDH-mutant glioblastoma, respectively; $P = 0.3$] and OS was

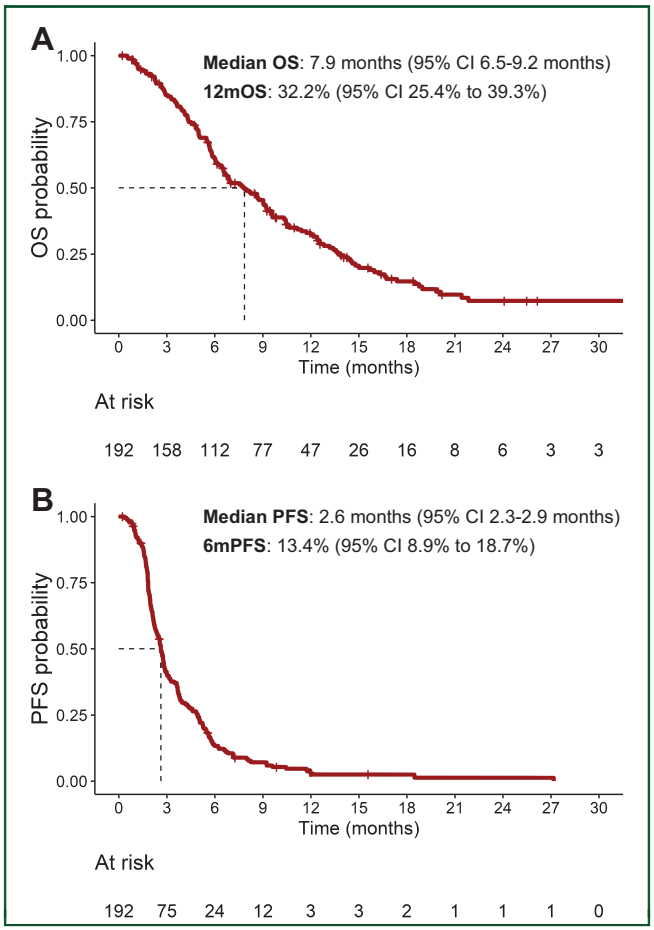

Figure 1. Kaplan–Meier plots for (A) overall survival (OS) and (B) progression-free survival (PFS).
6mPFS, 6-month progression-free survival; 12mOS, 12-month overall survival; CI, confidence interval.

7.8 months versus 13.5 months in patients with IDH wild-type and IDH-mutant glioblastoma ($P = 0.09$). Although the number of patients with IDH mutant was very small, none of them reported a radiologic response (0% versus 8.6% of patients with IDH wild type), whereas 16.7% of them showed SD (versus 15.7% of patients with IDH wild type).

Regarding safety, 43 patients (22.6%) experienced at least one regorafenib-related grade 3-4 adverse event, most commonly fatigue (5.8%), rash (4.7%), thrombocytopenia (2.6%) and increased serum alanine aminotransferase/aspartate aminotransferase (2.1%; Table 3). SAEs occurred in 1.6% of the treated study population. During the study, a dose reduction was required in 70 patients (36.8%). The most frequent reason for dose reduction was regorafenib-related adverse events in 87.6% of cases. Interruption/delay of regorafenib treatment was required in 85 patients (44.7%). None of the deaths were related to regorafenib treatment. Among the patients who experienced disease progression/relapse on regorafenib, 70.9% received third-line therapy. In approximately two-thirds of cases (65.4%), a nitrosourea-based regimen (fotemustine or lomustine) was used, 11 patients (14.1%) received bevacizumab, and 5 patients (6.4%) were treated with temozolomide rechallenge. Other treatments were given to 11 patients (14.1%).

Table 2. Best response to regorafenib treatment

Response (RANO criteria)	Values, *n* (%)
Disease control rate	39 (21.9)
Objective response rate	13 (7.3)
Complete response	0 (0)
Partial response	13 (7.3)
Stable disease	26 (14.6)
Progression disease	139 (78.1)

RANO, Response Assessment in Neuro-Oncology.

DISCUSSION

In this study, we reported a median OS very close to that seen in the REGOMA trial, confirming similar activity of regorafenib in the real-world setting. The REGOMA study,[8] a multicenter, randomized phase II clinical trial, showed promising survival results for regorafenib compared with lomustine therapy in patients with recurrent glioblastoma. Hence, the AIFA defined regorafenib as a reimbursable therapy[9] and it was also included in the National Comprehensive Cancer Network (NCCN) guidelines among the preferred treatments for patients with recurrent glioblastoma.[13] Subsequently, a few case reports and small retrospective studies explored the role of regorafenib with different results.[14-22] However, these results are of limited value due to the small sample size and the very heterogeneous clinical and histological characteristics of the cases analyzed (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.102943).

To our knowledge, the REGOMA-OSS is the largest prospective and observational study to evaluate the use of regorafenib in patients with first relapse/progression of glioblastoma in a real-world setting. In our multicenter study, 190 patients were enrolled and treated with regorafenib from 30 Italian centers. Patient characteristics, outcomes, and safety between the REGOMA study and our study are shown in Table 4, although the comparison between the two studies must be made with caution from a statistical standpoint, as they are two different studies. Clinical and molecular characteristics of the patients in our study appear to be rather similar to those of the REGOMA trial: some differences concern the average age of the enrolled patients (54.8 years in REGOMA study versus 58.5 years in REGOMA-OSS trial) and the use of corticosteroid therapy at the baseline (53% in REGOMA versus 59.5% in REGOMA-OSS). The median OS was 7.9 months (95% CI

Table 3. Drug-related adverse events

Grade 3-4 drug-related adverse events	Value, %
All	22.6
Fatigue	5.8
Skin rash	4.7
Thrombocytopenia	2.6
Hypertransaminasaemia	2.1
Hypertension	1.6
Hand–foot syndrome	1.6
Blood bilirubin increased	1
Others	3.2

Table 4. Comparison between the REGOMA trial and our study (REGOMA-OSS)

Characteristics	REGOMA	REGOMA-OSS
Patients, *N*	59	190
Age (years)	54.8	58.5
ECOG PS, %		
0	46	44.7
1	54	55.3
Corticosteroid use, %	53	59.5
Surgery at first recurrence, %	22	20.5
IDH mutated, %	5	7.5
MGMT methylated, %	49	50.3
Third-line therapy, %	68	70.9
Median OS (months)	7.4	7.9
Median PFS (months)	2	2.6
DCR, %	44	21.9
Grade 3-4 drug-related adverse events, %	56	22.6
Dose reduction, %	17	36.8
Dose delayed/discontinued, %	46	44.7
Drug-related death, %	0	0

DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; IDH, isocitrate dehydrogenase; MGMT, O^6-methylguanine-DNA methyltransferase; OS, overall survival; PFS, progression-free survival.

6.5-9.2 months), with a 12-month OS rate of 32.2% (95% CI 25.4% to 39.3%). These results appear to be comparable with those reported by the REGOMA trial where the median OS was 7.4 months (95% CI 5.8-12.0 months) with a 12-month OS of 38.9% (95% CI 26.6% to 51.0%).[8] Yet, the median PFS of our study (2.6 months, 95% CI 2.3-2.8 months) is also similar to the one in the REGOMA study (2.0 months, 95% CI 1.9-3.6 months). The reason for the lower rate of DCR in our study compared with the REGOMA trial (21.9% versus 44%) is unclear; specifically, we reported 7.3% and 14.6% of patients with PR and SD, respectively. Although the rate of patients with PR is higher compared with the REGOMA trial (7.3% versus 3%), patients reporting SD is much lower (14.6% versus 39%). This difference may be explained by the lack of centralized image review and a dedicated specialized neuroradiologist in a few of the participating centers without high expertise with the RANO criteria. Yet, the higher percentage of dose reductions in our study could also be the reason for the lower DCR compared with the REGOMA study.

In addition, results were recently presented at the Society of Neuro-Oncology (SNO) Congress in Vancouver, Canada, from the phase III Bayesian Adaptive Platform GBM AGILE trial in which patients with newly diagnosed unmethylated glioblastoma and patients with relapsed disease were treated with regorafenib. In the latter subgroup, regorafenib did not demonstrate superiority over lomustine in terms of OS: 9.4 months versus 10.1 months in the regorafenib and lomustine groups, respectively; HR 1.12).[23] Notably, patients with recurrent glioblastoma have shown similar survival with other treatments; the phase III Checkmate 143 trial of nivolumab versus bevacizumab reported a median OS of 10 months,[24] the EORTC 26101 trial did not show superiority of lomustine plus bevacizumab versus lomustine alone with a median OS of 9.1 months and 8.6 months, respectively[25]; the phase III REGAL study reported a survival range of 8-9.8 months in patients treated with lomustine, cediranib and cediranib plus lomustine[26]; finally, in another real-life study analyzing 36 Italian patients with recurrent glioblastoma treated with depatuxizumab mafodotin plus temozolomide, the median survival was 8.0 months.[27] Although median survival was very similar across trials, patients presented with heterogeneous clinical and molecular characteristics. In fact, patients taking steroids at baseline were 58% and 34% in REGOMA and EORTC 26101, respectively; ECOG PS was 0 in 46% of patients enrolled in REGOMA and 55% in REGAL; IDH was mutated in 2% and 4% in REGOMA and EORTC 26101, respectively, and MGMT methylation status was missing or undetermined in 1% and 48% in the latter two studies, respectively.

In the last version of the NCCN 2023 guidelines, bevacizumab and regorafenib were included as recommended regimens in patients with recurrent glioblastoma; however, bevacizumab never showed an increase in OS in randomized phase II/III studies in patients with recurrent glioblastoma, while bevacizumab plus lomustine showed to prolong PFS compared with lomustine alone; of note, in a Cochrane network meta-analysis, bevacizumab alone was not superior to lomustine in terms of PFS[28]; however, other meta-analyses have shown the potential role of bevacizumab alone in improving PFS.[29,30] Nevertheless, in an earlier systematic review and network meta-analysis, regorafenib ranked first in OS among other available second-line therapies for patients with recurrent glioblastoma; in fact, according to this study, patients receiving regorafenib are likely to have the longest OS (94% probability).[31]

Compared with lomustine, quality of life does not appear to be significantly different with regorafenib and bevacizumab.[32,33] In terms of SAEs, the Cochrane network meta-analysis showed no statistical difference in the rate of SAEs between regorafenib and lomustine in patients with recurrent glioblastoma, as opposed to other regimens such as bevacizumab plus lomustine, which had a higher incidence of SAEs,[28] while fotemustine (a nitrosourea drug like lomustine) did not show more toxicity compared with bevacizumab alone.[28] Yet, bevacizumab demonstrated a greater anti-edema effect than regorafenib, with a reduction in steroid dosage in ∼55%-58%[34,35] of cases (versus 6.5%-18% for regorafenib).[36]

Therefore molecular and clinical predictors may be useful to ensure a more effective, safe and personalized treatment; indeed, most studies have tried to identify these predictors for both bevacizumab and regorafenib therapy.[14,15,18,37-39] In our real-life study a significant proportion of patients do not respond to regorafenib (56% in REGOMA and 78% in REGOMA-OSS), highlighting the importance of patient selection. Some previous studies showed some biomarkers such as phosphorylated acetyl-CoA carboxylase and a specific molecular signature as predictors of regorafenib efficacy, but they need to be validated in other prospective studies.[14,15] Therefore to validate and implement the use of these biomarkers, an exploratory analysis will focus on molecular biomarkers as predictors of regorafenib in patients enrolled in the REGOMA-OSS trial.

In terms of safety, only 22.6% of treated patients in the REGOMA-OSS study reported grade 3-4 drug-related

adverse events, compared with a much higher percentage (56%) in the REGOMA study; yet the rate of the SAEs was lower in the present study: 1.6% versus 5% in the REGOMA trial. This important difference may be due to the higher rate of patients who had their regorafenib dose reduced due to drug-related adverse events (36.8% versus 17% in REGOMA); it is likely that most physicians would have opted for dose reduction at the first sign of adverse events in light of the clinical experience with regorafenib in this patient population over the past few years; in fact, although grade 3-4 adverse events were reported in only 22.6% of patients, the dose of regorafenib was reduced in a high proportion of cases (36.8%). By contrast, a recent smaller real-life observational study evaluated a different regorafenib schedule in a population of 66 patients with glioblastoma; the patients were treated with a gradually increasing dose from 80 to 160 mg in the first two cycles of therapy. With this 'modified' schedule, only 31.8% of treated patients reported grade 3-4 drug-related adverse events (versus 56% in the REGOMA study) maintaining a median OS of 7.1 months, a median PFS of 2.7 months (versus 7.4 months and 2.0 months in the REGOMA study, respectively) and a DCR of 40.1% (versus 44% in the REGOMA trial).[40]

Although the use of regorafenib in the REGOMA trial did not affect patients' quality of life compared with standard lomustine,[33] we are also analyzing quality of life data in the present study and will report the results in a future publication.

Regarding limitations, a weakness of our study could be the lack of independent and centralized neuroradiology and histopathology review; other potential limitations are the lack of molecular analyses in a small proportion of patients and the lack of standardized assessment of MGMT methylation status and IDH mutation status, as well as the use of remote monitoring due to the coronavirus disease 2019 period.

Conclusions

REGOMA-OSS is the largest prospective, observational, real-world study evaluating the activity and safety of regorafenib in patients with recurrent glioblastoma. We observed an improved toxicity profile compared with the REGOMA trial; the median OS was also similar to REGOMA and consistent with other previous studies. Molecular predictors of regorafenib efficacy need to be investigated to provide more personalized treatment.

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