CASE STUDY

Observational real-life study on regorafenib in recurrent glioblastoma: does dose reduction reduce toxicity while maintaining the efficacy?

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Abstract

Purpose In the phase 2 REGOMA trial, regorafenib improved overall survival, as compared with lomustine, in glioblastoma (GBM) patients at first progression after chemoradiation. Recently, some real-life trials showed similar impact on survival but a higher rate of adverse events than in REGOMA, thus raising concerns over tolerability. The aim of this study was to assess the efficacy and tolerability of a lower intensity regorafenib regimen.

Patients and methods Regorafenib daily dose was gradually increased from 80 to 160 mg across the first 2 cycles. Progression-free survival (PFS) and overall survival (OS) were defined as time from regorafenib initiation and disease progression or death.

Results Sixty-six GBM patients were included. Median age was 60.0 years. Median PFS and OS following regorafenib were 2.7 and 7.1 months, respectively. Best RANO response to regorafenib were partial response (PR) in 10 (15.1%), stable disease in 17 (25.8%), and progressive disease in 39 (59.1%) patients. Forty-six (69.7%) patients presented adverse events of any grade, and 21 (31.8%) grade 3–4 toxicity. In a multivariable analysis, higher age and absence of MGMTp methylation were significantly associated with poorer disease control after regorafenib.

Conclusions Our study is the largest observational real-life study on the use of regorafenib. Our lower intensity regimen proved as effective as the standard 160 mg daily schedule (mPFS and mOS being 2.7 vs 2.0 months and 7.1 vs 7.4 months in our study vs REGOMA, respectively). Moreover, we observed a higher rate of PRs as compared with REGOMA (15.0% vs 3.0%).

Keywords Regorafenib · Glioblastoma · Recurrence · Efficacy · Toxicity

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Background

Glioblastoma (GBM) is the most common primary brain tumour of the adult [1]. To date, the standard treatment of newly diagnosed GBM is maximal surgical resection followed by chemoradiation using temozolomide (TMZ) [2, 3]. However, disease progression occurs in almost all patients after first line treatment, and median overall survival (OS) is of the order of 20 months. [4] Since, no highly effective treatment has been found for disease recurrence, the choice of the best second-line therapy remains an open issue [5]. To date, the most employed medical treatments at recurrence consist of nitrosourea-based schedules and / or antiangiogenic therapy. Lomustine, a nitrosourea alkylating agent, has been used as control in several phase 2 and 3 trials [6–13], with a low objective response rate (around 10%), almost exclusively limited to patients with O6-methylguanine DNA methyltransferase promoter (MGMTp) methylation [8, 10, 12]. Bevacizumab is a recombinant humanised antibody that blocks angiogenesis by inhibiting the vascular endothelial growth factor receptor A (VEGF-A). As GBM is a highly vascularised tumour with increased endothelial proliferation and VEGFR expression [14], bevacizumab has been investigated in several trials in both newly diagnosed and recurrent GBM [15]. Overall, it has been shown to increase progression-free survival (PFS), but not OS [10].

Regorafenib is an oral inhibitor of several kinases involved in tumour angiogenesis (VEGFR1-3 and TIE2), oncogenesis (KIT, RET, RAF1, and BRAF), and in the interaction between tumour and microenvironment (platelet-stimulating factor 1 receptor [CSF1R]) [16–19]. Regorafenib was initially approved for metastatic colorectal cancer, advanced gastrointestinal stromal tumour (GIST), and advanced hepatocellular carcinoma (HCC) [20–22]. Following the demonstration of an antiangiogenic effect in a rat GS9L glioblastoma model [18], regorafenib was investigated in this setting as well. In the randomised, open-label, phase 2 REGOMA trial, GBM patients at first recurrence were treated with either regorafenib (160 mg daily 21/28 days) or lomustine [12]. Regorafenib improved OS (median OS: 7.4 vs 5.6 months, p = 0.0009) and PFS (6-month PFS: 16.9% vs 8.3%, p = 0.022) as compared with lomustine. Therefore, regorafenib was approved by different regulatory authorities as a second-line treatment for GBM patients. Recently, some real-life trials showed similar impact on survival but a higher rate of adverse events than in REGOMA, thus raising concerns over tolerability. [23–28]

The aim of this observational study designed in 2019 was to assess the efficacy and tolerability of a lower intensity regorafenib regimen in a real-life cohort of GBM patients at first progression.

Patients and methods

Inclusion criteria

Three Italian Institutions (Division of Neuro-Oncology, University and City of Health and Science Hospital, Turin; Department of Neurology and Brain Tumour Board AULSS2 Marca Trevigiana, Treviso; Division of Medical Oncology, University Hospital of Bari) participated to this non-sponsored prospective observational study. Patients ≥ 18 years with a histological diagnosis of glioblastoma at recurrence after first-line treatment were eligible. Second surgery at progression before regorafenib initiation was allowed. According to the 2016 World Health Organisation (WHO) both IDH-wildtype and IDH-mutant glioblastoma patients (astrocytomas grade 4, IDH-mutant according to the 2021 WHO Classification) were included. IDH mutation was assessed by Sanger sequencing, and MGMTp methylation by pyrosequencing or methylation-specific PCR. Additional inclusion criteria were: Karnofsky Performance Status (KPS) ≥ 60 and adequate bone marrow parameters. A history of hypertensive cardiopathy, cerebrovascular events, myocardial infarction or pulmonary embolism were criteria for exclusion.

This is an observational study. The Research Ethics Committee of the participating Institutions have confirmed that no ethical approval is required.

Treatment regimen

Regorafenib (tablets, 40 mg) was given orally, once per day, on a 3 weeks on / 1 week off schedule (21/28 days).

To improve drug tolerability and reduce adverse events, a dose escalation regimen was designed: the starting dose of the first cycle was 80 mg for 2 weeks, then 120 mg for 1 week; the starting dose of the second cycle was 120 mg for 2 weeks, then 160 mg. A daily dose of 160 mg was maintained from the third cycle on, if tolerated.

Adverse events were defined according to Common Toxicity Criteria for Adverse Events Version 5 (CTCAE v5.0) [29]. Dose reduction and/or cycle delay and/or interruption applied to patients with poor tolerability (grade 3–4 toxicity).

Magnetic resonance imaging (MRI) monitoring

MRI was performed every 3 months, or earlier in case of clinical deterioration. Response to regorafenib was evaluated on MRI according to RANO criteria [30].
MRI responses were assessed by neuroradiologists with an expertise in Neuro-Oncology in the participating Institutions.

**Endpoints**

The co-primary endpoints were PFS and OS, which were defined as time from regorafenib initiation to interruption due to recurrence/unacceptable toxicity (PFS) or death (OS). For patients with stable disease at the time of formal analysis, PFS and OS were measured from regorafenib initiation to the last visit (censoring).

The secondary endpoint was to evaluate drug tolerability.

**Statistical analysis**

Baseline characteristics of patients were summarised using median and interquartile range (IQR), and percentages and frequencies (n, %). Age at surgery was a surrogate of age at diagnosis.

The distribution of characteristics between patient subgroups were evaluated by the Mann–Whitney U test for continuous variables and the Chi-square test or Fisher’s exact test for categorical variables. Kaplan–Meier curves were drawn for PFS and OS and a Cox proportional hazard model was employed to estimate the crude and the multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for predictors of recurrence or survival.

The analysis was performed by IBM SPSS Statistics v.28 software.

**Results**

**Characteristics of the population and first-line treatment**

Sixty-six patients were enrolled in this observational study from January 2020 to February 2022. Median age was 60 years (57.0–63.0 95% CI). Median KPS was 70 (70.0–80.0 95% CI). Sixty-two patients had a diagnosis of GBM IDH-wildtype (93.9%), whereas 4 patients (6.1%) had astrocytomas IDH-mutant grade 4. MGMTp methylation was found in 30 patients (45.5%). Median PFS after first-line treatment was 9.3 months (7.4–11.1, 95% CI). Eight patients (12.1%) underwent second surgery at progression before regorafenib. Corticosteroids were used in 48 patients (72.7%) at baseline when regorafenib was started. The characteristics of the study population and first-line treatments are displayed in Table 1.

**Regorafenib regimen and response to treatment**

Regorafenib was prescribed with a mean dose of 93.3 mg/day during the first cycle, 133.3 mg/day during the second cycle, and 160 mg/day from the third cycle. However, as 20/66 (30.3%) patients needed a dose reduction due to poor tolerability, the mean regorafenib dose for the whole cohort from the third cycle was 147.8 mg daily. Overall, best RANO response on gadolinium-enhanced T1 sequences was partial response (PR) in 10 (15.2%), stable disease (SD) in 17 (25.8%), and progression of disease (PD) in 39 (59.1%) patients (Table 2). All 10 PRs were seen on the first MRI after three months of therapy: at the 6-months MRI that followed, 5/10 patients with initial PRs showed PD and 3/10 patients were stable. For the remaining 2 patients with initial PR it was not possible to assess the duration of the radiological response, as one patient interrupted regorafenib due to the occurrence of adverse events shortly after the 3-months MRI, and one had not yet undergone the 6-months evaluation at the time of formal analysis.

All PRs on gadolinium-enhanced T1 sequences in the enhancing areas displayed a SD in the T2/FLAIR sequences.

**Progression-free survival and overall survival following regorafenib**

Median time of follow-up was 6.8 months (range 1.0–24.8 months). At the end of the study, 63 (95.5%) patients were out-of-treatment: regorafenib was discontinued due to disease progression in 62 patients (93.9%), and drug-related toxicity in 1 patient (1.5%). The remaining 3 (4.5%) patients were still on treatment at the time of formal analysis. All progressions were local: no patient had multicentric progression or leptomeningeal spread.

Median PFS (mPFS) was 2.7 months (2.4–3.0 95% CI). PFS rate at 3, 6, 9 and 12 months was 45.0%, 11.0%, 7.0%, and 4.0%.

Median OS (mOS) was 7.1 months (5.4–8.9 95% CI), with an OS rate at 3, 6, 9 and 12 months of 86.0%, 61.0%, 40.0%, and 24.0%.

Thirty-nine patients (59.0%) underwent a third-line treatment at progression following regorafenib, as follows: fotemustine (18, 27.3%), lomustine and procarbazine (13, 19.7%), metronomic TMZ (3, 4.5%), second surgery (3, 4.5%), bevacizumab (1, 1.5%), and re-irradiation (1, 1.5%). Conversely, the remaining 24 patients (36.4%) were treated with best supportive care.

**Regorafenib-related toxicity**

Forty-six (69.7%) patients displayed regorafenib-related adverse events of any grade, while grade 3–4 adverse events were seen in 21 patients (31.8%). No treatment-related
deaths were observed. The median number of cycles for the development of adverse events was 1. The most common adverse events, regardless of CTCAE grade, were fatigue (22, 33.3%), hand-foot syndrome (18, 27.3%), elevated liver enzymes (10, 15.2%), thyroid toxicity (8, 12.1%), hypertension (8, 12.1%), and thrombocytopenia (7, 10.6%). The most common grade 3–4 adverse events were fatigue (6, 9.1%), hand-foot syndrome (5, 7.6%), and thrombocytopenia (4, 6.1%) (Table 3). The risk of regorafenib-related grade 3–4 adverse events was higher in patients with previous TMZ-related toxicity (HR 5.476, 1.320–22.712, p = 0.019), while it was not related to the duration of TMZ chemotherapy.

### Table 1 Characteristics of patient population

| Number of patients | 66 |
|--------------------|----|
| **Period**         | January 2020—February 2022 |
| **Median age, 95% CI** | 60.0 (57.0—63.0 95% CI) |
| **Median KPS, 95% CI** | 70.0 (70.0—80.0 95% CI) |
| **KPS = 60**       | 15 | 22.7% |
| **KPS = 70**       | 21 | 31.8% |
| **KPS = 80**       | 20 | 30.3% |
| **KPS = 90**       | 10 | 15.2% |
| **Sex**            |     |
| **Male**           | 38 | 57.6% |
| **Female**         | 28 | 42.4% |
| **MGMTp**          |     |
| **Unmethylated**   | 36 | 54.5% |
| **Methylated**     | 30 | 45.5% |
| **IDH status**     |     |
| **Wildtype**       | 62 | 93.9% |
| **Mutant**         | 4  | 6.1% |
| **First line treatment** | | |
| **RT/TMZ + TMZ**   | 61 | 92.4% |
| **6-week concurrent RT/TMZ** | 44 | 66.7% |
| **3-week concurrent RT/TMZ** | 17 | 25.8% |
| **TMZ upfront**    | 3  | 4.5% |
| **RT followed by TMZ** | 2  | 3.0% |
| **Adjuvant temozolomide** | | |
| **Median cycles, 95% CI** | 5.5 (3.0—7.0 95% CI) |
| **Toxicity with TMZ (any grade)** | 18 | 27.3% |
| **Grade 1—2**      | 13 | 19.7% |
| **Grade 3—4**      | 5  | 7.6% |
| **Thrombocytopenia** | 13 | 19.7% |
| **Neutropenia**    | 2  | 3.0% |
| **Elevated liver enzymes** | 1  | 1.5% |
| **Nausea/vomiting** | 1  | 1.5% |
| **Asthenia**       | 1  | 1.5% |
| **Best RANO response to 1st line treatment** | | |
| **PR**             | 10 | 15.2% |
| **SD**             | 28 | 42.4% |
| **PD**             | 28 | 42.4% |
| **mPFS after 1st-line treatment** | 9.3 months (7.4–11.1 95% CI) |
| **Re-resection prior to regorafenib** | 8 | 12.1% |
| **Steroids at baseline** | 48 | 72.7% |

CI coefficient index, CTCAE Common Toxicity Criteria for Adverse Events, IDH isocitrate dehydrogenase, KPS Karnofsky Performance Status, MGMTp O(6)-methylguanyl DNA methyltransferase promoter, PD progressive disease, PR partial response, RANO Radiological Assessment in Neuro-Oncology, RT radiotherapy, SD stable disease, TMZ temozolomide
In 20 (30.3%) patients, regorafenib-related toxicity was managed by keeping a dose of 120 mg/day. However, 9 (13.6%) patients needed a temporary interruption (ranging from 1 to 3 weeks) of treatment to recover from toxicity. Only in one case (1.5%) regorafenib was definitively interrupted due to thrombocytopenia grade 4.

Prognostic factors

In a univariate analysis of PFS following regorafenib, MGMT<sub>p</sub> methylation was the sole factor associated with a reduced risk of progression. In a univariate analysis of OS, MGMT<sub>p</sub> methylation was significantly associated with a prolonged OS, whereas use of steroids was associated with a shorter OS. However, in a multivariable analysis, MGMT<sub>p</sub> methylation only retained a prognostic importance on PFS and OS. Noteworthy, in a univariate analysis of survival, resection before regorafenib initiation did not significantly impact either mPFS (2.3 versus 2.7 months, p = 0.823) or mOS (8.9 versus 6.9 months, p = 0.924), nor did it influence the multivariable analysis (Table 4).

In a univariate analysis, mPFS of patients who received a reduced dose of 120 mg/day was slightly longer than that of patients who did not have any dose reduction (3.5 months, 2.5–4.5 95% CI, vs 2.5 months, 2.0–3.0 95% CI, p = 0.022). Likewise, mOS was slightly longer, even if not significantly, in case of dose reduction (9.2 months, 7.4–11.0 95% CI, vs 6.4, 5.3–7.5 95% CI, p = 0.184). Conversely, patients who needed a temporary interruption of treatment due to toxicity, as compared with those who did not, did not show significantly different mPFS (3.5 months, 2.3–4.7 95% CI, vs 2.6 months, 2.2–3.0 95% CI, p = 0.124) or mOS (9.2 months, 1.9–16.5 95% CI, vs 7.1 months, 5.5–8.7 95% CI, p = 0.938).

To explain why patients who received a reduced dose of regorafenib had a longer mOS, we explored the characteristics of this subgroup as compared with the other patients (Supplementary Table 1). We found that these patients had a higher prevalence of MGMT<sub>p</sub> methylation (13/20, 65.0%, versus 17/46, 37.0%, p = 0.035), underwent a longer period of TMZ chemotherapy before TMZ-failure (median TMZ cycles 8.0 versus 4.5, p = 0.046; time-to-TMZ failure 11.9 months vs 8.0 months, p < 0.001), and displayed a higher rate of objective RANO response to regorafenib (PRs being 6/20, 30.0%, vs 4/46, 8.7%, p = 0.021). Thus, some of these factors (especially the prevalence of MGMT<sub>p</sub> methylation) might have influenced the longer mPFS of this subgroup of patients. Finally, dose reduction did not retain a prognostic importance in a multivariable analysis on mPFS or mOS (Supplementary Table 2).

Discussion

Patients with GBM at recurrence show a dismal prognosis and scarce response to treatments. REGOMA was the first phase II trial to suggest the superiority of regorafenib over temozolomide in terms of mPFS (2.0 vs 1.9 months, with 16.9% vs 8.3% progression-free patients at 6 months, p = 0.022),

Table 2  Response to regorafenib according to RANO criteria, progression-free survival and overall survival

| Best RANO response to regorafenib | PR | 10 | 15.1% |
|----------------------------------|----|----|-------|
| SD                               | 17 | 25.8% |
| PD                               | 39 | 59.1% |
| mPFS following regorafenib       | 2.7 months (2.4–3.0 95% CI) |
| mOS following regorafenib        | 7.1 months (5.4–8.9 95% CI) |

mOS median overall survival, mPFS median progression-free survival, PD progressive disease, PR partial response, RANO Radiological assessment in neuro-oncology, SD stable disease

1.094, 0.967–1.236, p = 0.153), or patient age (HR 0.989, 0.943–1.037, p = 0.643).

Table 3  Regorafenib-related adverse events

| Event                                | Any grade | CTCAE grade 1–2 | CTCAE grade 3–4 |
|--------------------------------------|-----------|-----------------|-----------------|
| Fatigue                              | 22        | 33.3%           | 16              | 6               | 9.1%          |
| Hand-foot syndrome                    | 18        | 27.3%           | 13              | 5               | 7.6%          |
| Elevated liver enzymes               | 10        | 15.2%           | 8               | 2               | 3.0%          |
| Hypertension                          | 8         | 12.1%           | 7               | 1               | 1.5%          |
| Thyroid toxicity                      | 8         | 12.1%           | 7               | 1               | 1.5%          |
| Thrombocytopenia                      | 7         | 10.6%           | 3               | 4               | 6.1%          |
| Elevated pancreatic enzymes          | 3         | 4.5%            | 2               | 1               | 1.5%          |
| Diarrhoea                             | 2         | 3.0%            | 2               | 0               | 0.0%          |
| Oral mucositis                        | 2         | 3.0%            | 2               | 0               | 0.0%          |
| Thrombotic events                     | 2         | 3.0%            | 0               | 2               | 3.0%          |

CTCAE Common Toxicity Criteria for Adverse Events

 Springer
Multivariable analysis

Overall survival

Progression-free survival

Table 4 Univariate and multivariable analysis of survival following regorafenib

| Univariate analysis | Multivariable analysis |
|---------------------|------------------------|
|                     | Progression-free survival | Overall survival | Progression-free survival | Overall survival |
|                     | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value |
| Age 1.017 (0.995–1.039) | 0.136 | 1.022 (1.000–1.045) | 0.054 | 1.023 (0.996–1.051) | 0.091 | 1.020 (0.994–1.048) | 0.137 |
| MGMTp methylation 0.556 (0.327–0.947) | 0.031 | 0.458 (0.260–0.809) | 0.007 | 0.449 (0.246–0.819) | 0.009 | 0.433 (0.234–0.799) | 0.007 |
| Surgery prior to regorafenib 0.920 (0.435–1.946) | 0.827 | 1.040 (0.466–2.317) | 0.924 | 1.228 (0.552–2.735) | 0.614 | 1.585 (0.660–3.803) | 0.303 |
| KPS ≥ 70 at regorafenib initiation 0.704 (0.379–1.306) | 0.265 | 0.371 (0.196–0.700) | 0.002 | 0.856 (0.432–1.694) | 0.655 | 0.512 (0.252–1.038) | 0.063 |
| Use of steroids 1.060 (0.590–1.903) | 0.847 | 2.177 (1.023–4.630) | 0.043 | 0.730 (0.380–1.405) | 0.347 | 1.815 (0.824–3.995) | 0.139 |
| Regorafenib-related toxicity 0.775 (0.449–1.338) | 0.361 | 0.861 (0.478–1.551) | 0.618 | 0.794 (0.437–1.442) | 0.449 | 0.993 (0.522–1.890) | 0.983 |
| Objective RANO response to regorafenib 0.500 (0.237–1.055) | 0.069 | 0.945 (0.439–2.032) | 0.885 | 0.517 (0.235–1.138) | 0.101 | 1.502 (0.457–2.422) | 0.904 |

CI coefficient index, HR hazard ratio, KPS Karnofsky Performance Status, MGMTp O(6)-methylguanyl DNA methyltransferase promoter, RANO Radiological Assessment in Neuro-Oncology

and mOS (7.4 vs 5.6 months, with 38.9% vs 15.0% surviving patients at 12 months, p = 0.0009) [12]. Of note, the OS of patients treated with lomustine from REGOMA trial was remarkably short (5.6 months) as compared with that of patients included in the lomustine single-arms of the other randomised controlled trials (mOS ranging from 7.1 months to 10.4 months [6, 10, 31]), which could imply an overestimation of regorafenib efficacy.

Aside from REGOMA, few other studies have investigated the efficacy and tolerability of regorafenib at recurrence: to date, an observational real-life study on 54 patients and few smaller retrospective series have been published (Table 5) [12, 23–28]. Therefore, we are presenting the largest real-life observational study that has been performed so far.

The baseline characteristics of patients from our cohort were similar to those of patients included in other large studies [12, 23]. However, some differences should be mentioned: first, patients from our cohort had a higher median age (60 years) than those from REGOMA (54.8 years) and from the larger observational real-life study (56 years) [23]. Also, patients with MGMTp methylation included in our study (30/66, 45.5%) were slightly less represented than in REGOMA trial (29/59, 49.0%) and the observational real-life study (28/54, 52.8%). [23]

As in REGOMA trial, we included glioblastoma patients treated with regorafenib as second-line treatment. We also included a small subgroup (4, 6.1%) of patients with IDH-mutant high-grade astrocytomas, formerly defined as glioblastomas IDH-mutant by the 2016 WHO Classification, which was our reference when the study was started. Likewise, in the REGOMA trial few patients with GBM IDH-mutant were included (2/59, 3.4%): however, in this trial the IDH status was unknown in 15/59 (25.4%) patients, which could disclose a significant underestimation of IDH-mutant tumours with more indolent clinical course [12]. Patients with GBM IDH-mutant were 5/54 (9.3%) in the observational real-life trial from Lombardi et al., [23] whereas other retrospective studies included more heterogeneous cohorts of patients with both GBM IDH-wildtype and lower-grade gliomas IDH-mutant. [24–28]

In our study, we employed for the first time a dose escalation protocol to improve patient tolerability and compliance. We reported a lower rate of adverse events of any grade (69.7%) according to CTCAE v5.0 as compared with other real-life studies (90.7%—100.0%) [23, 24, 27]. Similarly, we observed a lower rate of adverse events grade 3–4 (31.8%) compared with other series (53.0–83.3%) [24, 27, 28]. Furthermore, we reported a reduced incidence of some adverse events that were described as frequent complications in other studies: for example, the incidence of liver enzymes elevation was lower in our series than in REGOMA trial (15.2% vs 48.0%), as well as that of hypertension (12% vs 22%), low platelet count (10.6% vs 20.0%), hypothyroidism (12.1% vs 19.0%), or increased pancreatic enzymes (4.5% vs 20.0%); on the other hand, we reported a higher incidence of fatigue (33.3% vs 24.0%) and a similar incidence of hand-foot syndrome (27.3% vs 22.0%) as compared with REGOMA.
Table 5 Regorafenib in clinical studies—a review of the literature

| Author           | Study design | No. of pts | Median age | Type of tumour | Indication for starting regorafenib | Prior treatments before starting regorafenib | Dose | Best RANO response | Adverse events according to the CTCAE v5.0 | mPFS from starting regorafenib | mOS from starting regorafenib |
|------------------|--------------|------------|------------|----------------|-------------------------------------|---------------------------------------------|------|---------------------|------------------------------------------|-----------------------------|-----------------------------|
| Lombardi et al., 2019 | Phase II ‘REGOMA’ | 59 | 54.8 years | GBM IDH-wildtype: 42, 71.2% | First relapse after 1st-line treatment | First-line treatment Surgery + RT/ TMZ + TMZ: 59, 100.0% | 160 mg daily | PD: 6, 100.0% | Any grade: 33, 56.0% | Grade 3–4: 13, 22.0% | 2.0 months | 7.4 months |
|                  |              |            |            | GBM IDH-mutant (a): 2, 3.4% |                       |                              |      |                        |                                           |                             |                            |
|                  |              |            |            | IDH status unknown: 15, 25.4% |                       |                              |      |                        |                                           |                             |                            |
|                  |              |            |            | MGMTp-non methylated: 30, 51.0% |                       |                              |      |                        |                                           |                             |                            |
|                  |              |            |            | MGMTp-methylated: 29, 49.0% |                       |                              |      |                        |                                           |                             |                            |
| (a) According to 2016 WHO Classification
| Kebir et al., 2019 | Retrospective | 6 | 47 years | GBM IDH-wildtype: 4, 66.4% | Later stage of disease (all > 2 relapses) | Surgery: 6, 100.0% RT: 6, 100.0% TMZ: 6, 100.0% Lomustine: 6, 100.0% Other CHT: 3, 50.0% | 160 mg daily | PD: 6, 100.0% | Any grade: 6, 100.0% | Grade 3–4: 5, 83.3% | 3.5 months | –5.5 months |
|                 |              |            |            | Astrocytoma grade 3 IDH-wildtype: 1, 16.7% |                       |                              |      |                        |                                           |                             |                            |
|                 |              |            |            | Astrocytoma grade 3, IDH-mutant: 1, 16.7% |                       |                              |      |                        |                                           |                             |                            |
|                 |              |            |            | MGMTp-methylated: 4, 66.4% |                       |                              |      |                        |                                           |                             |                            |
|                 |              |            |            | MGMTp-methylated: 2, 33.6% |                       |                              |      |                        |                                           |                             |                            |
| Author          | Study design | No. of pts | Median age | Type of tumour | Indication for starting regorafenib | Prior treatments before starting regorafenib | Dose | Best RANO response | Adverse events according to the CTCAE v5.0 | mPFS from starting regorafenib | mOS from starting regorafenib |
|-----------------|--------------|------------|------------|----------------|-------------------------------------|-----------------------------------------------|------|-------------------|------------------------------------------|-------------------------------|-------------------------------|
| Zeiner et al., 2019 | Retrospective | 21         | 49 years   | GBM: 17, 81.0% | Recurring GBM (regardless of no. of previous treatments) | Median no. of previous surgery: 1 (range 0–3) | 160 mg daily | Dose reduction due to adverse events: 4, 19.0% (mean dose of the whole cohort considering patients with dose reduction: not specified) | SD: 2/19, 10.5% | Not specified | 14 weeks |
| Tzaridis et al., 2019 | Retrospective | 24         | 54 years   | GBM IDH-wildtype: 19, 79.5% | Later stage of disease First relapse: 3, 12.5%, Second relapse: 9, 37.5%, Third to seventh relapse: 12, 50% | Lomustine: 21, 87.5% Temozolomide: 7, 29.2% Bevacizumab: 5, 20.8% Experimental IDH-inhibitor: 1, 4.1% | 80—160 mg daily (mean dose not specified) | PR: 3, 13.0% | SD: 3, 13.0% | Not described | 2.1 months | 4.2 months |
Table 5 (continued)

| Author                | Study design     | No. of pts | Median age | Type of tumour                                      | Indication for starting regorafenib | Prior treatments before starting regorafenib | Dose            | Best RANO response | Adverse events according to the CTCAE v5.0 | mPFS from starting regorafenib | mOS from starting regorafenib |
|-----------------------|------------------|------------|------------|----------------------------------------------------|-------------------------------------|---------------------------------------------|-----------------|-------------------|---------------------------------------|-------------------------------|-------------------------------|
| Lombardi et al., 2021 | Observational real-life | 54        | 56 years   | GBM IDH-wildtype: 49, 90.7% GBM IDH-mutant (a): 5, 9.3% MGMTp-methylated: 28, 52.8% MGMTp-non methylated: 25, 47.2% (a) According to 2016 WHO Classification | First relapse after 1st-line treatment | First-line treatment Surgery + RT/ TMZ + TMZ: 59, 100.0% Treatment at recurrence before regorafenib Second surgery: 16, 29.6% | 160 mg daily Dose reduction due to adverse events: 20, 37.0% (mean dose of the whole cohort considering patients with dose reduction: not specified) | PR: 4, 7.4% SD: 21, 38.9% PD: 29, 53.7% | Any grade: 49, 90.7% Grade 3–4: 13, 24.0% | 2.3 months | 10.2 months |
| Treiber et al., 2022  | Retrospective    | 11         | 53 years   | GBM: 10, 90.9% Astrocytoma grade 3: 1, 9.1% IDH-wildtype: 8, 72.7% IDH-mutant: 3, 27.3% MGMTp-methylated: 9, 81.8% MGMTp-non methylated: 2, 18.2% | First relapse: 6, 54.6% Second (or further) relapse: 5, 45.4% | First-line treatment Surgery + RT/ TMZ + TMZ: 5, 45.4% Surgery + RT + TMZ/ lomustine (CeTeG NOA09): 6, 54.6% Treatment at recurrence(s) before regorafenib Second surgery: 6, 54.6% | 160 mg daily Dose reduction due to adverse events: 5, 45.4% (mean dose of the whole cohort considering patients with dose reduction: not specified) | PR: 1, 9.0% SD: 3, 23.3% PD: 4, 36.4% NA (due to treatment discontinuation before MRI): 3, 23.3% | Any grade: 11, 100.0% Grade 3–4: 6, 54.6% | Time-to-treatment failure (TTF)—defined as time from starting regorafenib to death, progressive disease, or cessation of treatment due to other reasons (e.g. side effects): 3.3 months |
Table 5 (continued)

| Author               | Study design | No. of pts | Median age | Type of tumour                                                                 | Indication for starting regorafenib | Prior treatments before starting regorafenib | Dose      | Best RANO response | Adverse events according to the CTCAE v5.0 | mPFS from starting regorafenib | mOS from starting regorafenib |
|----------------------|--------------|------------|------------|--------------------------------------------------------------------------------|---------------------------------------|---------------------------------------------|---------|-------------------|-------------------------------------------|-------------------------------|-----------------------------|
| Werner et al., 2022  | Retrospective| 30         | 54 years   | GBM, *IDH*-wildtype: 24, 79.0%                                                | First relapse: 8, 27.0%               | Surgery + RT/ TMZ: 22, 73.0%                | 160 mg daily Dose reduction due to adverse events: 9, 29.0% (mean dose of the whole cohort considering patients with dose reduction: 148 mg) | Not specified | Any grade: not specified Grade 3–4: 16, 53.0% | 2.6 months                  | 6.2 months                    |
**Table 5** (continued)

| Author Study design | No. of pts | Median age | Type of tumour | Indication for starting regorafenib | Prior treatments before starting regorafenib | Dose | Best RANO response | Adverse events according to the CTCAE v5.0 | mPFS from starting regorafenib | mOS from starting regorafenib |
|---------------------|------------|------------|-----------------|-------------------------------------|-----------------------------------------------|------|-------------------|------------------------------------------|-------------------------------|-------------------------------|
| Present study, 2022 | Observational | 66 | 60 years | GBM IDH-wildtype: 62, 93.9% | First relapse after 1st-line treatment | First-line treatment | Escalation dose protocol | PR: 10, 15.1% SD, 17, 25.8% PD: 39, 59.1% | 2.7 months | 7.1 months |
|                     |             |            | Astrocytoma, IDH-mutant, grade 4: 4, 6.1% | Surgery + RT/ TMZ + TMZ: 61, 92.4% | Surgery + RT + TMZ: 2, 3.0% | Surgery + TMZ: 3, 4.5% | Mean dose 1st cycle: 93.3 mg daily | Mean dose 2nd cycle: 133.3 mg daily | Mean dose from the 3rd cycle: 160 mg daily (147.8 mg considering 20 patients, 30.3%, who had dose reduction from 160 to 120 mg due to poor tolerability) | | |
|                     |             |            | MGMTp-non methylated: 36, 54.5% | | | | | | | |
|                     |             |            | MGMTp-methylated: 30, 45.5% | | | | | | | |

*CHT*, chemotherapy, *CTCAE v5.0* Common Terminology Criteria for Adverse Events version 5.0, *IDH* isocitrate dehydrogenase, *KPS* Karnofsky Performance Status, *MGMTp* O(6)-methylguanoyl DNA methyltransferase promoter, *PD* progressive disease, *PR* partial response, *pts* patients, *RANO* Radiological Assessment in Neuro-Oncology, *RT* radiotherapy, *SD* stable disease, *TMZ* temozolomide
Interestingly, we found a significant association between the development of grade 3–4 adverse events and a previous history of temozolomide-related adverse events during the first line of treatment, which may help to identify which patients are at higher risk of toxicity with regorafenib.

What is of critical importance is that dose reduction did not negatively affect treatment efficacy in our cohort. In fact, the mPFS from our study (2.7 months) was similar to that reported in REGOMA trial (2.0 months) and other studies (2.1–3.5 months) [23–28]. Noteworthy, mPFS spans in a quite narrow gap (2–3.5 months) across different studies, also depending on the different timing of the MRI monitoring (either 2 or 3 months).

Conversely, OS after regorafenib shows a slight variation across different studies. In our study, the mOS was similar to REGOMA trial (7.1 months vs 7.4 months), and longer than that reported in the retrospective series by Kebir et al. (about 5.5 months) [24], Zeiner et al. (14 weeks) [25], Tzarisidis et al. (4.2 months) [26], and Werner et al. (6.2 months) [28]. The shorter survival of patients included in the smaller series was probably a consequence of the use of regorafenib in patients with advanced disease and/or after two or more relapses. Conversely, patients included in the observational real-life study from Lombardi et al. had a longer mOS (10.2 months) as compared with patients included in the other series (including ours) [23]. In this case, the longer survival was partly due to a prevalence of patients with higher performance status who underwent second surgery before starting regorafenib (16/54, 29.6%).

We observed a higher proportion of objective RANO responses as compared with other studies. We reported 10 PRs out of 66 patients (15.1%), whereas CRs and PRs were 1/59 and 2/59 respectively (overall, 5.0%) in REGOMA trial, and PRs were 4/54 (7.4%) in the observational study by Lombardi et al. In our study all PRs were observed within the first 3 cycles of treatment, and were rarely maintained over time. In the next future, the use of advanced MRI (with integration of perfusion and diffusion-weighted imaging with ADC) and/or amino acidic PET will help to identify cases of pseudoresponse, as some initial data have suggested. [25, 32]

Whether some biological factors are associated with a higher benefit from regorafenib is under investigation. To date, some molecular markers have been proposed as predictors of response to regorafenib in two post-hoc analyses on patients from the REGOMA trial. First, a mini-signature of 2 gene transcripts (HIF1A, CDKN1A) and 3 miRNAs (miR-3607-3p, miR-301a-3p, miR-93-5p) was associated with a prolonged survival after regorafenib [33]. Second, the phosphorylation of the acetyl-CoA carboxylase (pACC), a surrogate of the activation of the AMPK pathway, has been suggested to prolong the mOS of patients on regorafenib, but not lomustine (mOS 9.3 months vs 5.5 months, p = 0.0013) [34]. These preliminary data are of interest, as the identification of molecular predictors of response may help to select patients who can benefit from regorafenib.

Finally, the AGILE trial, which is currently investigating the role of regorafenib in patients with newly diagnosed GBM without MGMTp methylation, will help to clarify some open issues by collecting prospective data from a controlled population of patients. [35]

Conclusion

Our study is the largest observational real-life study on the use of regorafenib in a cohort of GBM patients at first recurrence. We employed an escalation dose protocol that was useful to reduce regorafenib-related toxicity and improve compliance, while proving as effective as the standard schedule.

Long-lasting responses to regorafenib are rare, and probably limited to patients with peculiar clinical and molecular features. Also, to define criteria for pseudoresponse or pseudoprogression following regorafenib is needed to better evaluate the MRI response.

The ongoing AGILE trial will address many open issues in a larger prospective cohort of patients.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval This is an observational study. The Research Ethics Committees of the participating Institutions have confirmed that no ethical approval is required.

Consent to participate Informed consent to collect and analyse clinical and pathological/molecular data was obtained from all subjects who were alive at the time of start of the study or from relatives in case of death of the subjects, according to ethics regulations for observational studies of each local Ethics Committee.
References

1. Ostrom QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS (2021) CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2014–2018. Neuro-Oncology 23(Supplement_3):iii1–iii105. https://doi.org/10.1093/neuonc/noab200

2. Stupp R, Mason WP, van den Bent MJ et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352(10):987–996. https://doi.org/10.1056/NEJMoa043330

3. Stupp R, Hegi ME, Mason WP et al (2009) Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 10(5):459–466. https://doi.org/10.1016/S1470-2045(09)70025-7

4. Delgado-López PD, Corrales-García EM (2016) Survival in glioblastoma: a review on the impact of treatment modalities. Clin Transl Oncol 18(11):1062–1071. https://doi.org/10.1007/s12094-016-1497-x

5. Fazzari FGT, Rose F, Pauls M et al (2022) The current landscape of systemic therapy for recurrent glioblastoma: a systematic review of randomized-controlled trials. Crit Rev Oncol Hematol 169:103540. https://doi.org/10.1016/j.critrevonc.2021.103540

6. Wick W, Puduvalii VK, Chamberlain MC et al (2010) Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. J Clin Oncol 28(7):1168–1174. https://doi.org/10.1200/JCO.2009.23.2595

7. Batchelor TT, Mulholland P, Neyns B et al (2013) Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma. J Clin Oncol 31(26):3212

8. Taal W, Oosterkamp HM, Walenkamp AM et al (2014) Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. Lancet Oncol 15(9):943–953

9. Brandes AA, Carpentier AF, Kesari S et al (2016) A phase II randomized study of galunisertib monotherapy or galunisertib plus lomustine compared with lomustine monotherapy in patients with recurrent glioblastoma. Neuro Oncol 18(8):1146–1156

10. Wick W, Gorlia T, Bendszus M et al (2017) Lomustine and bevacizumab in progressive glioblastoma. N Engl J Med 377(20):1954–1963

11. Duerinck J, Du Four S, Bouttens F et al (2018) Randomized phase II trial comparing axitinib with the combination of axitinib and lomustine in patients with recurrent glioblastoma. J Neurooncol 136(1):115–125

12. Lombardi G, De Salvo GL, Brandes AA et al (2019) Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): a multicentre, open-label, randomised, controlled, phase 2 trial. Lancet Oncol 20(1):110–119. https://doi.org/10.1016/S1470-2045(18)30675-2

13. Van Den Bent M, Eoli M, Sepulveda JM et al (2020) INTEL-LANCE 2/EORTC 1410 randomized phase II study of Deapturn-M alone and with temozolomide vs temozolomide or lomustine in recurrent EGFR amplified glioblastoma. Neuro Oncol 22(5):684–693

14. Wong ML, Prawira A, Kaye AH, Hovens CM (2009) Tumour angiogenesis: its mechanism and therapeutic implications in malignant gliomas. J Clin Neurosci 16(9):1119–1130

15. Zhang T, Xin Q, Kang JM (2021) Bevacizumab for recurrent glioblastoma: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 25(21):6480–6491. https://doi.org/10.26355/eurrev_202111_27092

16. Schmieder R, Hoffmann J, Becker M et al (2014) Regorafenib (BAY 73–4506): antitumor and antimitastatic activities in preclinical models of colorectal cancer. Int J Cancer 135(6):1487–1496

17. Abou-Elkacem L, Arns S, Brix G et al (2013) Regorafenib inhibits growth, angiogenesis, and metastasis in a highly aggressive, orthotopic colon cancer model. Mol Cancer Ther 12(7):1322–1331

18. Wilhelm S, Dumas J, Adnane L et al (2011) A new oral multi-kinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer 129(1):245–255

19. Zopf D, Fichtner I, Bhargava A et al (2016) Pharmacologic activity and pharmacokinetics of metabolites of regorafenib in preclinical models. Cancer Med 5(11):3176–3185

20. Grothey A, Van Cutsem E, Soehrobo A et al (2013) Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 381(9863):303–312

21. Demetri GD, Reichardt P, Kang YK et al (2013) Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 381(9863):295–302

22. Bruix J, Qin S, Merle P et al (2017) Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 389(10064):56–66

23. Lombardi G, Caccese M, Padovan M et al (2021) Regorafenib in recurrent glioblastoma patients: a large and monocentric real-life study. Cancers 13(18). https://doi.org/10.3390/cancers13184731

24. Kebir S, Rauschenbach L, Radbruch A et al (2019) Regorafenib in patients with recurrent high-grade astrocytoma. J Cancer Res Clin Oncol 145(4):1037–1042. https://doi.org/10.1007/s00432-019-02868-5

25. Zeiner PS, Kinzig M, Divé I et al (2019) Regorafenib CSF penetration, efficacy, and MRI patterns in recurrent malignant glioma patients. J Clin Med. https://doi.org/10.3390/jcm812031

26. Tzardis T, Gepfner-Tuma I, Hirsch S et al (2019) Regorafenib in advanced high-grade glioma: a retrospective bicentric analysis. Neuro Oncol 21(7):954–955. https://doi.org/10.1093/neuonc/noz071

27. Treiber H, von der Brelic E, Malinova V, Mielke D, Rohde V, Chapuy CI. Regorafenib for recurrent high-grade glioma: a unicentric retrospective analysis of feasibility, efficacy, and toxicity. Neurosurg Rev, https://doi.org/10.1007/s10143-022-01826-z

28. Werner JM, Wolf L, Tischer C et al (2022) Efficacy and tolerability of regorafenib in pretreated patients with progressive CNS grade 3 or 4 gliomas. J Neuro-Oncol. https://doi.org/10.1007/s11060-022-04066-9

29. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events. Version 5.0. Published November 27, 2017. Published online 2020.

30. Wen PY, Macdonald DR, Reardon DA et al (2010) Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. JCO 28(11):1963–1972. https://doi.org/10.1200/JCO.2009.26.3541

31. Weller M, Le Rhun E (2020) How did lomustine become standard of care in recurrent glioblastoma? Cancer Treat Rev 87:102029. https://doi.org/10.1016/j.ctrv.2020.102029

32. Gallidikis N, Werner JM, Tischer C, Fink GR, Langen KJ (2019) Imaging findings following regorafenib in malignant gliomas: FET PET adds valuable information to anatomical MRI. Neurooncol Adv. https://doi.org/10.1093/noan/vdz038

33. Santangelo A, Rossato M, Lombardi G et al (2021) A molecular signature associated with prolonged survival in glioblastoma
patients treated with regorafenib. Neuro Oncol 23(2):264–276. https://doi.org/10.1093/neuonc/noaa156
34. Indraccolo S, De Salvo GL, Verza M et al (2020) Phosphorylated acetyl-CoA carboxylase is associated with clinical benefit with regorafenib in relapsed glioblastoma: REGOMA trial biomarker analysis. Clin Cancer Res 26(17):4478–4484. https://doi.org/10.1158/1078-0432.CCR-19-4055
35. Alexander BM, Ba S, Berger MS et al (2018) Adaptive global innovative learning environment for glioblastoma: GBM AGILE. Clin Cancer Res 24(4):737–743

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