Clinical activity of regorafenib in elderly patients with recurrent glioblastoma

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Received July 14, 2022; Accepted November 10, 2022

DOI: 10.3892/mco.2023.2605

Abstract. Glioblastoma multiforme is one of the most frequent and aggressive primary tumors in the central nervous system, representing >60% of all brain tumors in adults. Despite treatment, prognosis remains poor with most if not all patients experiencing disease recurrence and a 2-year survival rate of 27%. At present, no confirmed standard treatment exists for recurrent glioblastoma. Regorafenib is one of the few options available, based on results from the REGOMA trial. In the present study, a real-life retrospective investigation on the role of regorafenib in patients with recurrent glioblastoma (>60 years old) from two main Oncological Units in South Italy (Azienda Ospedaliera Universitaria Luigi Vanvitelli, Naples, Italy and Ospedale Civile San Giovanni di Dio, Frattamaggiore, Naples, Italy), was performed. The primary endpoint was overall survival (OS), whereas progression-free survival (PFS), objective response rate and disease control were secondary endpoints. Survival was then analyzed according to age, isocitrate dehydrogenase (IDH) and methylated methylguanine-DNA-methyltransferase (MGMT) status. A total of 56 patients met the eligibility criteria. The intention to treat population median PFS (mPFS) was 4.1 months and median OS (mOS) was 6.8 months. Age did not appear to have a significant influence on mPFS. mOS in MGMT-methylated patients was improved compared with that of the unmethylated group (7.7 months vs. 5.6 months). Both mOS and mPFS were longer in IDH-mutant patients. The present study was one of the first real life analyses of regorafenib in recurrent glioblastoma. The results were in line with the REGOMA trial. Age did not appear to be a prognostic factor, thus suggesting that treatment choice should not be different in elderly. MGMT methylation appeared to influence OS. To the best of our knowledge, this was the first report of regorafenib activity in older patients and, while the results were statistically significant, these should be confirmed in further studies.

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Key words: regorafenib, glioblastoma, isocitrate dehydrogenase, methylated methylguanine-DNA-methyltransferase (MGMT), elderly

Introduction

Glioblastoma multiforme (GBM) is one of the most frequent and aggressive primary tumors in the Central Nervous System (CNS), representing more than 60% of all brain tumors in adults (1,2).

In over 90% of cases GBM occurs de novo (primary GBM) without evidence of a less malignant precursor and usually grows more rapidly and has a worse prognosis than secondary GBM, developing from lower grade astrocytoma or oligodendrogliomas.

GBM remains incurable with a poor prognosis both for limited therapeutic alternatives and for high risk of progression or recurrence. The median overall survival (mOS) is about 15 months with 2- and 1-year survival rate respectively of 27 and 41%; only GBM associated with methylated methylguanine-DNA-methyltransferase (MGMT) gene reach a mOS about 24 months; however, less than 10% of patients survives at 5 years (3-5).

In newly diagnosed GBM, the standard of care (SoC) is surgical resection followed by concomitant chemoradiotherapy (CRT) with temozolomide (6) and subsequently adjuvant chemotherapy (5,7-10). However, relapse rate remains poor, with most relapses occurring around 6-9 months after primary treatment (5,11).

In case of recurrence, treatment options are scarce and include re-surgery, re-irradiation, traditional chemotherapeutic drugs, alone or in combination, such as nitrosourea compounds like fotemustine or CCNU (lomustine), temozolomide rechallenge, or antiangiogenic drugs such as bevacizumab, all with limited efficacy (9,12). In addition, immune-checkpoint inhibitors, such as nivolumab or pembrolizumab, have shown poor results. There is no uniform consensus on standard treatment and even the guidelines fail to facilitate therapeutic decision in recurrent setting; therefore, enrollment in clinical trials is recommended. In several countries, Lomustine is usually used in second line after temozolomide failure, with mOS range of 8.6-9.8 months and median progression-free survival (mPFS) of 1.5-2.7 months (13,14).

Fotemustine is the only third generation of nitrosourea available In Italy, and has achieved encouraging results, though with low-certainty evidence (15).

Regorafenib is a small-molecule multi-kinase inhibitor already approved in second-line therapy for advanced hepatocellular carcinoma (HCC) (16,17) and in third-line treatment both for advanced colorectal cancer (CRC) (18-20) and gastrointestinal stromal tumors (GISTs) (20). Since 2019, regorafenib has been approved by Agenzia Italiana del Farmaco (AIFA)in recurrent glioblastoma as second line therapy, following the results of a phase 2 trial by Lombardi *et al* (21) (REGOMA). REGOMA is a randomised, comparative, multicenter phase 2 trial designed to evaluate the efficacy of regorafenib in this setting, compared to lomustine. In this trial, 119 patients were randomized to receive either regorafenib or lomustine. At the median follow-up of 15.4 months, OS, primary endpoint of the study, was greatly improved in the regorafenib group vs. SoC cohort (7.4 vs. 5.6, respectively). The disease control rate (DCR) was 44% in the regorafenib arm and 20% in the lomustine control arm. Because of this, regorafenib has been approved in Italy and, while sometimes used in other countries on a single patient basis as an off label treatment, it is conspicuously absent from European Association of Neuro-Oncology (EANO) (9).

Although the REGOMA trial has brought new hope in patients with GBM, it presents some critical issues related to both the absence of a phase 3 study, necessary to confirm the results obtained, and to the mOS of patients treated with lomustine found to be inferior to what is known in literature in the same population (8,6-9,3 months). This underlines the importance of stratifying GBM based on key molecular alterations and/or specific prognostic factors.

Moreover, elderly GBMs often present with a dismal prognosis, with survival around 6 months, and a limited response to treatments. Several molecular features are being investigated and different prognostic assessment including age, performance status (PS), disease burden, comorbidities and other factors have been proposed to better predict outcomes and prognosis (22).

We report our findings based on a retrospective analysis of a cohort of 56 patients >60 years treated in two Units in South Italy, Azienda Ospedaliera Universitaria Luigi Vanvitelli (Naples) and Ospedale Civile San Giovanni di Dio (Frattamaggiore, Naples). It is one of the few studies following REGOMA trial to study regorafenib in a real-life environment and one of the few to do so with a homogeneous ITT population: all patients were diagnosed with recurrent glioblastoma and treatment was initiated in a second line setting. We chose to focus on elderly patients, defined as patients >60 years, since median age of diagnosis of glioblastoma is 64 years, with many diagnoses being made in 70 years or older patients (23), and seeing how for these patients is harder not only to participate in clinical trials but also to receive SoC therapy, due to worsening clinical conditions, increasing comorbidities, and reduced social network.

Materials and methods

Study design and participants. Ours was a bi-centric retrospective study analyzing the role of regorafenib in recurrent glioblastoma patients >60 years. All data were collected retrospectively.

Inclusion criteria were designed to be as close as possible to a real-life setting: histologically confirmed Glioblastoma diagnosis, prior therapy according to Stupp protocol, adequate bone marrow, liver, and renal function. Performance status (PS) was measured according to the Eastern Cooperative Oncology Group (ECOG), and only patients with PS 0-2 were considered eligible to treatment (alas, from fully active patients to capable of self-care but not to any work).

Exclusion criteria were all those of routine clinical practice: previous therapy for recurrent disease, arterial thrombotic or embolic events within six months, uncontrolled hypertension, myocardial infarction, need for antiviral treatment for active hepatitis B or C, contemporary use of strong cytochrome P3A4 inhibitors or inducers. We included in our ITT population Isocitrate Dehydrogenase (IDH) mutant Glioblastomas, mostly secondary glioblastomas, although the newest 2021 WHO classification of CNS tumors define Glioblastomas strictly as IDH wild type (24): our decision was based on the time of initial diagnosis, due to the different classification criteria; furthermore, IDH mutant patients were present in the REGOMA trial population (21).

Methylated methylguanine-DNA-methyltransferase (MGMT) methylation and IDH mutational status were assessed on archived tumor tissue in separate laboratories for each center. MGMT methylation status was assessed by methylation array by EPIC array Illumina 850k according to Bady *et al* (25) or Methylation Specific PCR (MSP/PCR) as per Vlassenbroeck *et al* (26) after bisulfite modification of DNA, while IDH mutations status was assessed by methylation array by EPIC array Illumina 850k (25) or immunohistochemistry (27).

Unfortunately, information regarding previous treatment or molecular analysis is not available for all patients, as some of them were initially treated elsewhere and, due to the retrospective nature of the study, it was difficult to retrieve all data.

Procedures. Regorafenib was administered as per product label: 160 mg of regorafenib (four 40 mg tablets) per day

Table I. Baseline ITT population characteristics (n=56).

Variable	Value
Median age at regorafenib start, years	68 (60-79)
Sex, n (%)	
Male	37 (66.07)
Female	19 (33.93)
ECOG PS, n (%)	
0	17 (30.36)
1	30 (53.57)
2	9 (16.07)
Surgery at time of recurrence, n (%)	5 (8.90)
IDH status, n (%)	
IDH mutated	3 (5.36)
IDH wild type	32 (57.14)
Unknown	21 (37.50)
MGMT status, n (%)	
MGMT methylated	24 (42.86)
MGMT unmethylated	20 (35.71)
Unknown	12 (21.43)
Corticosteroid use, n (%)	
Yes	48 (85.71)
No	8 (14.29)
Third line treatment following PD, n (%)	
Yes	19 (33.93)
No	37 (66.07)

All data are presented as the median (range) or absolute number (%). ECOG PS, Eastern Cooperative Oncology Group performance status; IDH, isocitrate dehydrogenase; ITT, intention to treat; MGMT, methylated methylguanine-DNA-methyltransferase; PD, progressive disease.

Table II. AEs during regorafenib treatment.

AEs	Grade 1	Grade 2	Grade 3
Hand foot skin reaction, n	3	1	2
Rash/desquamation, n	1	2	0
Piastrinopenia, n	0	5	2
Neutropenia, n	2	0	0
Hypertension, n	3	3	0
Fatigue, n	9	10	2
Voice changes, n	1	5	1
Vomiting, n	1	3	0
Hepatic AEs, n	1	2	0
Aspartate aminotransferase elevation, n	1	3	2
Hyperbilirubinemia, n	4	0	0
Proteinuria, n	2	3	1
Fever, n	4	0	0
Cardiac, n	1	2	0
Diarrhea, n	4	1	0
Total, n (%)	37 (43)	40 (46)	10 (11)

A total of 87 AEs were reported, none of grade 4. 25% of all-comers population (14 out of 56 patients) did not report any toxicities. AEs, adverse events.

orally for three weeks in a four-week cycle. Dose reductions were allowed in case of toxicities on a 40 mg scale basis to a minimum of 80 mg/day (50% dose reduction). Treatment was continued until disease progression (according to Response Assessment in Neuro-Oncology-RANO-Criteria), unacceptable toxicities, death, or consent withdrawal.

Outcomes. Primary endpoint was OS, while PFS, objective response rate (ORR) and proportion of patient achieving disease control (DC) were secondary endpoints. OS was defined as time from treatment start to death from any cause, PFS as time from treatment start to disease progression or death, ORR as partial (PR) or complete response (CR) according to RANO criteria and disease control as SD, PR or CR according to RANO criteria. OS and PFS were estimated with Kaplan-Meier methods. Survival data were then stratified according to age, IDH mutation and MGMT methylation status.

Statistical analysis. Patient characteristics were reported as median with range of values between parentheses for continuous variables and percentages for categorical variables. Kaplan Meier estimates helped computing survival curves, whereas survival differences were evaluated using the log-rank test, with significance level of P=0.05. Statistical analyses were performed using IBM SPSS statistics v.23.0.

Results

Patients. Data were collected from 2019 to 2021 and fifty-six patients were included in the final analysis (Tables I and II), 19 female and 37 males; median age at start of treatment was 68 years (60-79 years). Patients showed mainly an ECOG PS of 1, as expected due to the diagnosis and the advanced setting.

IDH and MGMT data were available for most patients. IDH mutations were identified only in 3 out of 35 patient whose mutational status was known, whereas MGMT was found methylated in 24 patients and unmethylated in 20 patients; for the remaining 12, MGMT methylation status was unknown.

Survival outcomes. Longest treatment period with regorafenib was for 8 cycles. At cut-off date (25/03/2022), none of the enrolled patients were still treated with regorafenib and only three patients were not reported dead (two alive, still in treatment; one lost at follow up). 19 patients were treated at regorafenib progression with a third line therapy, 17 with fotemustine and 2 with lomustine. mPFS was estimated as 4.0 months (95% IC 3.1-5.0) (Fig. 1) and mOS as 6.8 (95% IC 5.6-8.0) (Fig. 2). Data were than stratified for MGMT status and for age.

No significant difference was found between the two populations based on MGMT status in mPFS (3.1

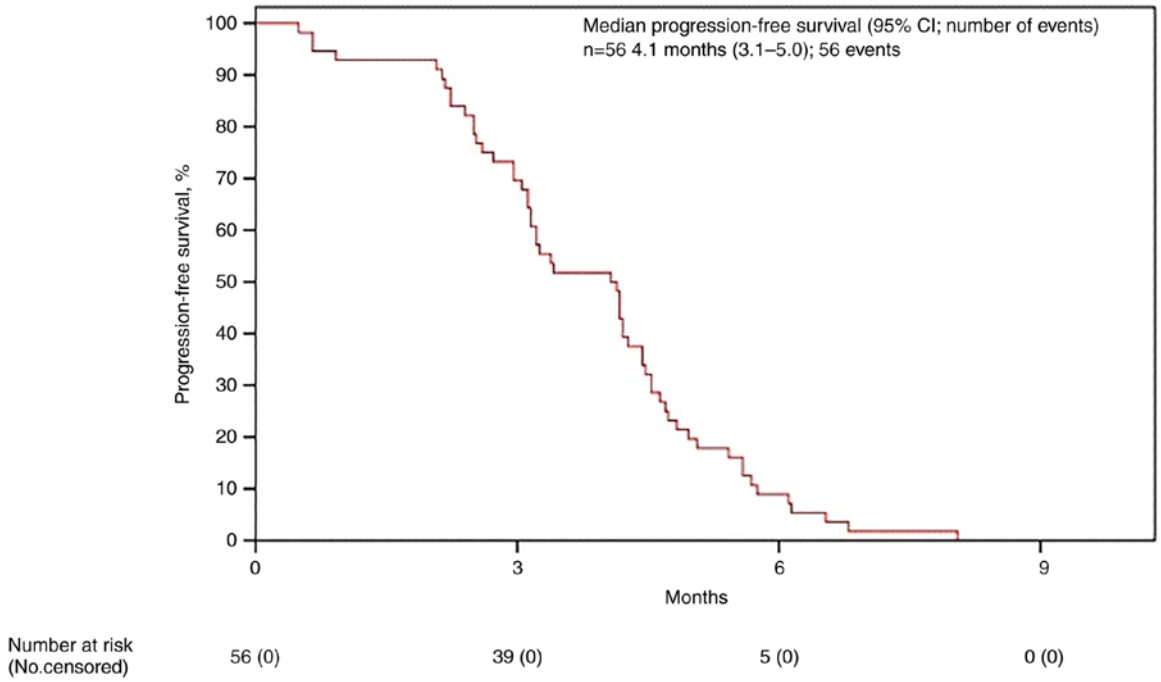

Figure 1. Median progression-free survival was estimated to be 4.1 months.

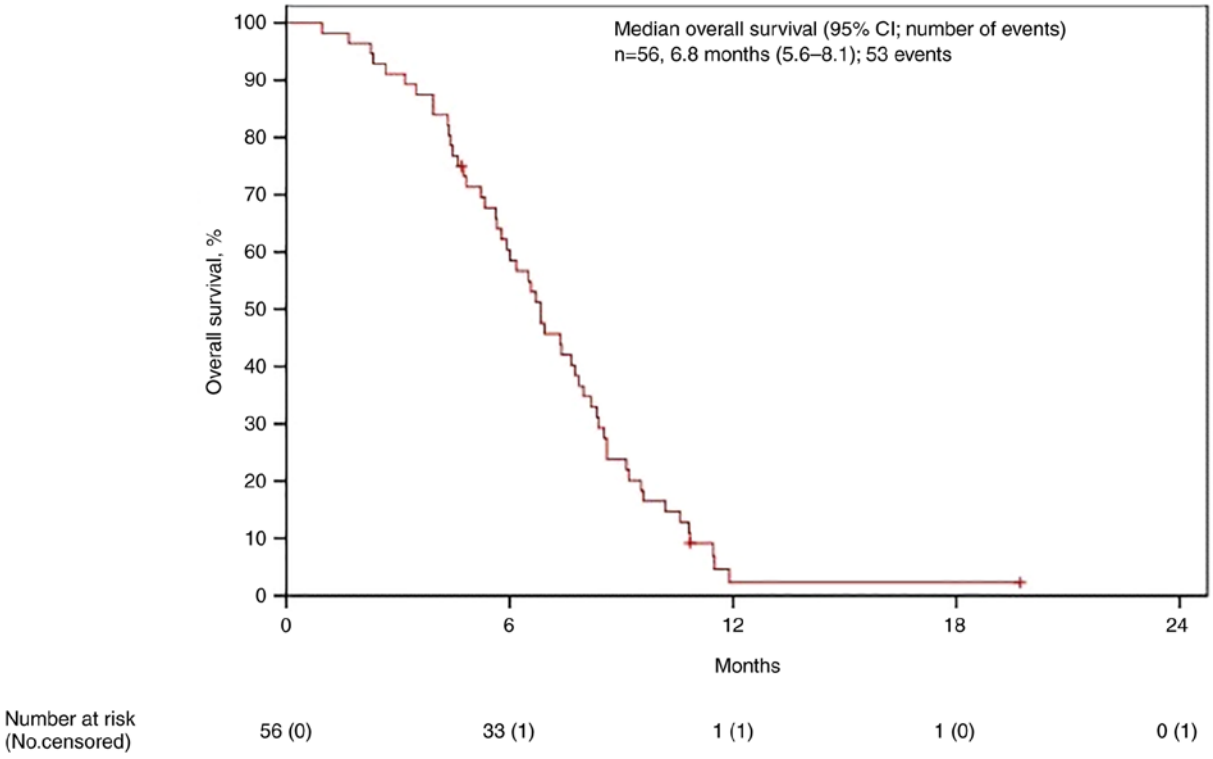

Figure 2. Median overall survival was estimated to be 6.8 months.

months vs. 4.1 months, P 0.170) (Fig. 3), whereas mOS in MGMT methylated patient was statistically significant superior to that of the unmethylated group, 7.7 months (5,29-6,01) vs. 5.6 months (5,29-6,01), P 0.048 (Fig. 4.)

Age did not appear to be a significant influence on PFS. We stratified ITT population according to age twice: one time using 65 years as cut-off, a second time using 70 years. Patients aged >65 years were 39, whereas patients with >70 years were 18. Neither study showed any significance difference of mPFS between the two populations (P 0.074 using 65 years as cut-off, P 0.332 using 70 years).

Other clinical measures. Adverse events (AEs) were recorded for all almost patients and only 25% of the ITT (14 patients)

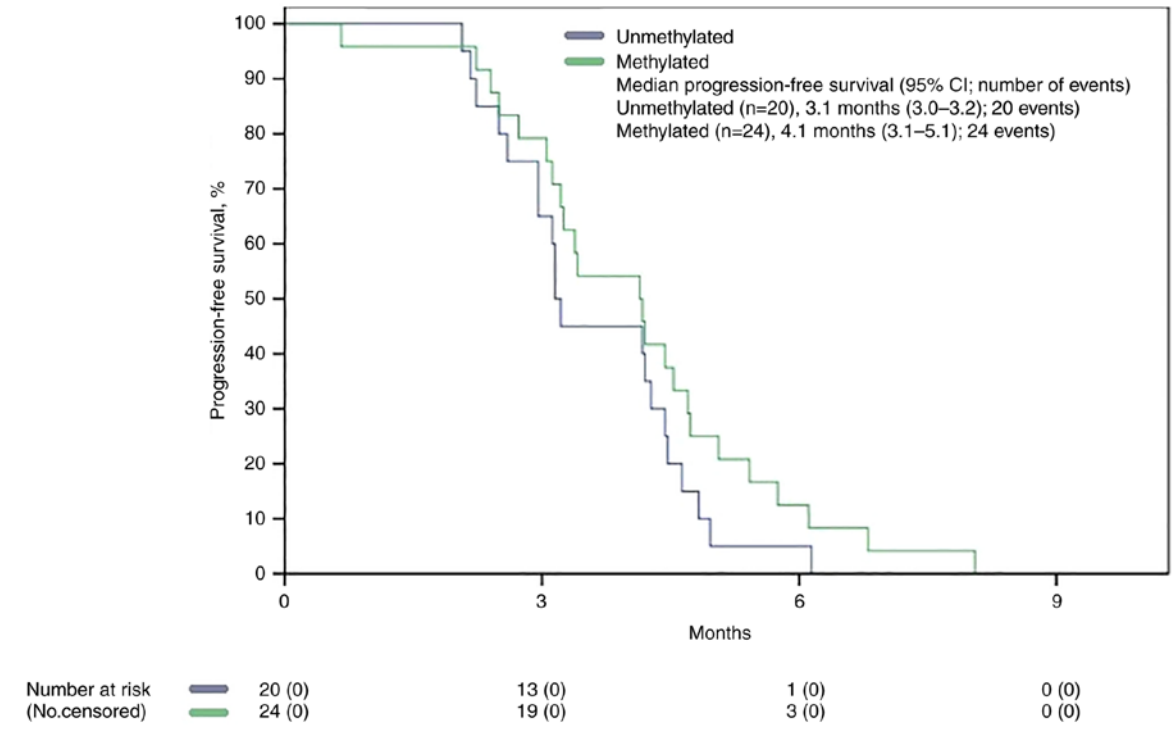

Figure 3. Median progression-free survival stratified for methylated methylguanine-DNA-methyltransferase promoter methylation status.

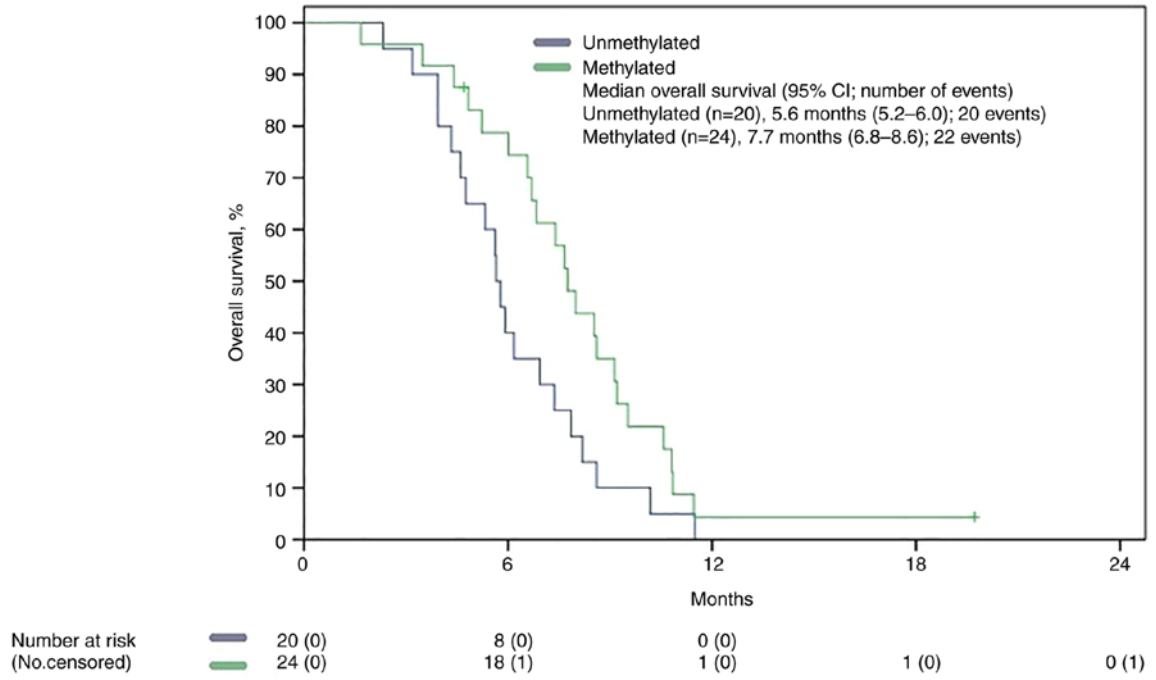

Figure 4. Median overall survival stratified for methylated methylguanine-DNA-methyltransferase promoter methylation status.

did not report any toxicities. Eighty-seven AEs were reported totally: of these, the majority were grade 2 (46%) and grade 1 (43%) according to Common Terminology Criteria for Adverse Events (CTCAE) scale, with only 10 grade 3 events (11%). No patient reported grade 4 AEs. The only grade 3 reported AEs were hand-foot skin reactions (HFSR), piastrinopenia, fatigue, voice changes, proteinuria, and aminotransferase elevation. Most reported toxicities (>5%) have been fatigue (24%), piastrinopenia (8%), voice changes (8%), HFSR (7%), hypertension (7%), proteinuria (7%), aspartate aminotransferase (AST) elevation (7%) and diarrhea (6%). (Table III).

Nearly half of the ITT population (44.6%) needed dose reduction, due to AEs or clinical condition, to improve tolerability and allow for treatment continuation. Out of the 25 patients who needed reductions, dose was lowered to 80 mg per day for three of them.

Table III. Best response during regorafenib treatment.

Outcome	No. (%)
Partial response	5 (8.9)
Complete response	0 (0.0)
Stable disease	22 (39.3)
Progressive disease	29 (51.8)

Objective response rate, 8.9%; disease control rate, 48.2%. Neuroradiological assessment was carried out according to the Response Assessment in Neuro-Oncology criteria.

Out of the 56 patients, none was reported as having a CR, 5 patients (8.9%) developed PR and 22 patients (39.3%) showed stable disease (SD) as their best response. DCR was then 48.2% with an ORR of 8.9%. 29 patients (51.8%) developed progressive disease at their first MRI imaging (Table IV).

Discussion

To our knowledge, this was one of the few analyses following REGOMA to study regorafenibas treatment at first recurrence in glioblastoma patients in a real-life setting and possibly the only one to focus on an older population. Median age of patients treated with regorafenib in REGOMA was 54.8 years (46.8-61.3), whereas in our project median age reached 68 years. (60-79). Although appearing small, our sample size is comparable to other publications in the same setting due to the relative incidence and prognosis of glioblastoma. Thus, we believe our results to be representative of a real life population.

Our results were mostly comparable to those of REGOMA, with a DCR of 48% (vs. 44%), although our patients only showed SD or PR with no CR.CR were instead reported in REGOMA trial in 2% of patients. It must be noted that neither a subsequent prospective study by Lombardi *et al* (28) published in 2021 nor a 2019 bicentric retrospective analysis by Tzaridis *et al* (29) showed evidence of CR; indeed, a 2019 retrospective analysis by Kebir *et al* (30) on six high grade astrocytomas showed a DCR of 0%.

mOS was slightly lower in our findings, 6.8 months vs. 7.4 months, easily due to an older and more comorbid population than that of the REGOMA trial and, of course, to the characteristics of a real-life retrospective setting, that allows for less stringent inclusion criteria. Anyhow, results were largely superimposable, confirming the benefit of regorafenib on OS on the ITT.

At the same time, mPFS was then doubled in our study, 4.0 months vs. 2.0 months. Kebir *et al* (30) also showed a higher mPFS (3.5 months) compared to REGOMA. As in that case, our discordant results may be due to the nature of the study: being a bicentric retrospective analysis, MRI time schedule was easily dependent on investigators choices and variable on a case-to-case basis, thus determining a formally higher result.

As reported above, mOS was found statistically superior in patients with methylated MGMT promoter (mOS 7.7 months vs. 5.6 months), with no difference in mPFS (mPFS 3.1 months vs. 4.1 months). MGMT promoter methylation has been since long identified as a predictive factor of increased survival from alkylating agents (9,31). Unfortunately, no benefit has yet been identified in patients treated with regorafenib (9,28). While our data need to be evaluated in other studies, especially prospective trials with larger populations, one must consider the possibility of the two subgroups being unbalanced for confounder factors, determining such a result. Indeed, while the proportion of patient in the two subgroups that completed at least 6 cycles of temozolomide is quite similar (50% in the unmethylated group vs. 62.5% in the methylated group), there was a higher percentage of patient that underwent radical surgery at diagnosis in the latter group (77% vs. 41%).

Age did not appear to be a prognostic factor, with no difference in mPFS in the two subgroup analysis performed. This is consistent with previous results from Lombardi *et al* (28) real-life trial and may help considering older patients with good performance status for treatment with regorafenib, irrespective of age. Furthermore, if we compare our results to those of Lombardi regarding ORR, they are largely superimposable. DCR reached 48% in our study compared to 46% in the latter, whereas ORR resulted 9 to 7.4% (28).

Our study may help in referring older patients with good PS to treatment with regorafenib, irrespective of age, especially since our population, although significantly older (median age of 68 years vs.55 years of Lombardi trial or 54.8 years of REGOMA trial), presented similar survival and control rates.

Survival was also analyzed according to IDH status, but our results cannot be generalized due to the strong unbalance between the two groups, with only 3 patients reporting a mutation in IDH (data similar to that of REGOMA trial with only 2 patients in the regorafenib arm and 0 in the lomustine arm). Survival was prolonged in the IDH mutant population, with a mPFS of 6.1 months and mOS of 11.5 months vs. respectively 3.1 and 6.1 months in the IDH wild type group (mOS p 0.041; mPFS p 0.009). Mutations in IDH have been generally reported in so-called secondary glioblastomas (32) and are an important prognostic factors associated with longer OS, although, as specified before, the new WHO system does not allow for IDH mutant glioblastoma but classifies them into astrocytomas (grade 2 to 4) or oligodendrogliomas (grade 2 or 3) (24).

Regorafenib was overall well tolerated in our population, with mainly grade 1 and 2 AEs. Only 25% of the ITT (14 patients) did not report any toxicities. 56% of the patients in Regorafenib arm developed at least one grade 3-4 AE in the REGOMA trial and 90% ported at least one all-grade drug-related toxicity in a subsequent study by Lombardi *et al* (28): with this in mind, one must consider the possibility of low accuracy in toxicity reports for this study. Even adjusting for this eventuality, safety profile was comparable to other trials involving regorafenib, both in glioblastoma and in other setting, thus advocating for its use in older but medically fit patients as a real therapeutic alternative.

The only grade 3 reported AEs were HFSR, piastrinopenia, fatigue, voice changes, proteinuria, and aminotransferase elevation. HFSR accounted for 7% of overall AEs (11% of the ITT, 6 patients) with only 2 patients showing grade 3 AEs. Incidence is thus lower than what was reported in REGOMA trial (grade 1-2, 22%, grade 3, 10%) or other trials in GBM (29), which was even lower than data from CORRECT (33) and RESORCE (34) trials (overall HFS rate 47% in the CORRECT trial and 53% in the

Table IV. Patient data.

Patient	Year of birth	Age at diagnosis, years	Sex	ECOG PS	IDH1/2	MGMT	Surgery	Date of surgery	Type of surgery	No. of adjuvant TMZ cycles	Date of recurrence	Second surgery	Second radiotherapy	CCS	Regorafenib start	Dose reduction	Best response to regorafenib	Recurrence date after regorafenib	Therapy at recurrence	Date of death
P001	1945	71	F	2	Unknown	Methylated	Yes	NA	Partial	11	May-19	No	No	No	Dec-19	Yes	PD	Feb-20	No	Mar-20
P002	1950	69	M	1	Unmutated	Methylated	Yes	May-20	Complete	6	Apr-21	No	No	No	Apr-21	Yes	SD	Aug-21	Fotemustine	Oct-21
P003	1948	70	M	1	Unknown	Methylated	Yes	Jan-19	Complete	6	Jan-20	Yes	Yes	Yes	Feb-20	Yes	SD	Jun-20	Fotemustine	Dec-20
P004	1980	63	M	0	Unmutated	Methylated	Yes	Apr-20	Complete	12	Nov-21	No	No	No	Dec-21	No	PD	Dec-21	No	Jan-22
P005	1951	68	M	1	Unmutated	Unmethylated	Yes	Nov-19	Complete	6	Dec-20	No	No	No	Dec-20	No	PD	Mar-21	No	May-21
P006	1953	66	M	1	Unmutated	Unmethylated	Yes	Jun-20	Complete	6	Aug-21	No	No	No	Aug-21	No	SD	Jan-22	No	Feb-22
P007	1954	64	M	1	Unmutated	Methylated	No			6	Apr-20	No	No	No	Apr-20	Yes	PD	Aug-20	Fotemustine	Nov-20
P008	1952	66	F	2	Unknown	Unknown	No			1	Jan-20	No	No	No	Feb-20	No	PD	Jul-20	No	Sept-20
P009	1950	67	M	1	Unknown	Methylated	Yes	Sept-18	Partial	6	Aug-19	No	No	No	Sept-19	Yes	SD	Feb-20	No	Mar-20
P010	1957	61	M	1	Unmutated	Unmethylated	No			4	May-19	No	No	No	May-19	Yes	PD	Aug-19	No	Nov-19
P011	1956	62	M	2	Unmutated	Unknown	Yes	Jun-19	Partial	NA	Oct-21	No	No	No	Nov-21	No	PD	Dec-21	No	Dec-21
P012	1950	69	M	1	Unmutated	Methylated	Yes	Nov-19	Partial	4	Aug-20	No	No	No	Sept-20	Yes	PD	Dec-20	No	Jan-21
P013	1952	66	M	1	Mutated	Unmethylated	Yes	May-19	Partial	6	Mar-20	No	No	No	Mar-20	No	SD	Aug-20	No	Sept-20
P014	1962	65	M	0	Unknown	Unmethylated	Yes	Aug-18	Partial	2	Jul-19	No	No	No	Aug-19	No	PD	Oct-19	No	Nov-19
P015	1958	59	M	2	Unmutated	Unmethylated	Yes	Mar-18	Complete	16	Oct-19	No	No	No	Nov-19	Yes	PD	Feb-20	No	Feb-20
P016	1947	70	M	1	Unknown	Unknown	Yes	Jul-2018	Partial	9	Feb-21	No	No	No	Apr-21	Yes	SD	Sept-21	Lomustina	Alive
P017	1958	60	M	1	Unmutated	Unmethylated	Yes	Jul-19	Partial	3	Feb-20	Yes	Yes	Yes	Mar-20	Yes	SD	Aug-20	Fotemustine	Nov-20
P018	1951	68	F	0	Unmutated	Methylated	Yes	Feb-20	Complete	6	Apr-21	Yes	Yes	Yes	Apr-21	No	PD	Aug-21	No	Oct-21
P019	1959	60	F	1	Unknown	Unmethylated	Yes	Aug-19	Partial	4	Jun-20	No	No	No	Jul-20	Yes	PD	Oct-20	No	Nov-20
P020	1948	70	F	1	Unknown	Unknown	Yes	Na	Partial	NA	Jan-20	No	No	No	Jan-20	No	PD	May-20	No	Sept-20
P021	1947	72	M	0	Unmutated	Unmethylated	Yes	May-20	Partial	3	Feb-21	No	No	No	Mar-21	No	PD	May-21	No	Jun-21
P022	1947	71	M	2	Unmutated	Methylated	Yes	Dec-18	Partial	6	Sept-19	No	No	No	Oct-19	No	SD	Mar-20	Fotemustine	Jul-20
P023	1957	66	F	1	Unknown	Unknown	Yes	Na	Partial	NA	Nov-20	No	No	No	Nov-20	No	SD	Jun-21	No	Aug-21
P024	1949	70	M	1	Unknown	Methylated	Yes	Jul-20	Complete	3	Mar-21	No	No	No	Mar-21	Yes	SD	Aug-21	Fotemustine	Feb-22
P025	1948	70	M	2	Unmutated	Methylated	Yes	Nov-19	Complete	6	Sept-20	No	No	No	Sept-20	No	PR	Mar-21	No	Apr-21
P026	1951	68	M	1	Unmutated	Unmethylated	Yes	Jul-20	Partial	6	Aug-21	No	No	No	Aug-21	Yes	PD	Oct-21	No	Jan-22
P027	1946	72	F	1	Unmutated	Methylated	Yes	Sept-19	Complete	6	Aug-20	No	No	No	Sept-20	No	SD	Feb-21	Fotemustine	May-21
P028	1957	64	M	1	Unknown	Unknown	Yes	Na	Partial	NA	May-19	No	No	No	May-19	No	PD	Aug-19	No	Oct-19
P029	1952	67	F	0	Unknown	Unknown	Yes	Jan-20	Complete	6	Mar-21	No	No	No	Mar-21	No	SD	Oct-21	No	Jan-22
P030	1955	64	F	0	Unmutated	Unmethylated	Yes	Feb-20	Complete	5	Jan-21	No	No	No	Feb-21	Yes	SD	Jul-21	Fotemustine	Dec-21
P031	1951	66	M	0	Unmutated	Unmethylated	Yes	Oct-18	Complete	6	Sept-19	No	No	No	Sept-19	Yes	SD	Mar-20	Fotemustine	Jun-20
P032	1951	67	F	1	Unknown	Unmethylated	Yes	Jan-19	Complete	6	Dec-19	No	No	No	Dec-19	Yes	PD	Apr-20	No	May-20
P033	1949	69	M	0	Unknown	Methylated	Yes	Mar-19	Complete	5	Jan-20	No	No	No	Feb-20	No	PD	Jun-20	No	Oct-20
P034	1951	68	M	0	Unmutated	Methylated	Yes	Jun-20	Complete	3	Feb-21	No	No	No	Feb-21	No	PD	May-21	Fotemustine	Oct-21
P035	1962	75	F	1	Unknown	Unknown	Yes	Na	Partial	NA	Dec-19	No	No	No	Dec-19	No	PD	Dec-19	No	Feb-20
P036	1978	59	M	1	Mutated	methylated	Yes	Oct-18	Partial	0	Jul-20	No	No	No	Jul-20	Yes	SD	Mar-21	Fotemustina	Alive
P037	1953	65	F	0	Unmutated	Methylated	Yes	Mar-19	Complete	6	Jan-20	No	No	No	Feb-20	Yes	PD	May-20	Fotemustine	Oct-20
P038	1957	62	M	0	Unknown	Methylated	No			3	Oct-20	No	No	No	Nov-20	No	PR	Jun-21	Fotemustine	Sept-21
P039	1947	72	F	0	Unknown	Methylated	Yes	Aug-20	Complete	6	Oct-21	Yes	Yes	Yes	Oct-21	No	SD	Feb-22	No	Alive
P040	1943	76	F	0	Unmutated	Unmethylated	Yes	May-20	Complete	6	Jun-21	No	No	No	Jun-21	Yes	SD	Oct-21	No	Jan-22

Table IV. Continued.

Patient	Year of birth	Age at diagnosis, years	Sex	ECOG PS	IDH1/2	MGMT	Surgery	Date of surgery	Type of surgery	No. of adjuvant TMZ cycles	Date of recurrence	Second surgery	Second radiotherapy	CCS	Regorafenib start	Dose reduction	Best response to regorafenib	Recurrence date after regorafenib	Therapy at recurrence	Date of death
P041	1948	71	M	2	Unmutated	Unknown	Yes	Oct-20	Partial	0	Mar-21	No	No	No	Apr-21	Yes	PD	May-21	No	Jul-21
P042	1949	70	M	0	Unmutated	Unmethylated	Yes	Jan-20	Partial	4	Nov-20	No	No	No	Nov-20	Yes	PD	Feb-21	No	Apr-21
P043	1948	70	M	1	Unmutated	Unmethylated	Yes	Feb-19	Complete	6	Jan-20	No	No	No	Feb-20	Yes	PD	May-20	Fotemustine	Sept-20
P044	1947	72	M	0	Unmutated	Unmethylated	Yes	Jan-20	Complete	5	Nov-20	No	No	No	Nov-20	No	SD	Apr-21	No	May-21
P045	1953	66	M	1	Unmutated	Methylated	Yes	Jul-20	Complete	5	Apr-21	No	No	No	May-21	No	PD	Aug-21	No	Dec-21
P046	1940	78	M	0	Unknown	Methylated	Yes	Dec-19	Complete	6	Dec-20	No	No	No	Dec-20	No	SD	May-21	Fotemustine	Sept-21
P047	1951	65	F	1	Unknown	Unknown	Yes	Na	Partial	NA	Dec-20	No	No	No	Dec-20	No	PD	Mar-21	No	Apr-21
P048	1957	62	M	2	Mutated	Unmethylated	Yes	Nov-19	Complete	6	Nov-20	No	No	No	Nov-20	Yes	SD	Jun-21	Fotemustine	Nov-21
P049	1954	64	M	0	Unmutated	Methylated	Yes	Feb-19	Complete	6	Jan-20	No	No	No	Feb-20	No	PR	Jul-20	Fotemustine	Jan-21
P050	1948	70	M	1	Unmutated	Methylated	Yes	Oct-18	Complete	3	Jun-19	No	No	No	May-19	No	PD	Aug-19	No	Oct-19
P051	1944	75	M	1	Unmutated	Unmethylated	No			2	Apr-20	No	No	No	May-20	Yes	PD	Jul-20	No	Sept-20
P052	1959	59	F	1	Unmutated	Methylated	Yes	Nov-18	Complete	6	Nov-19	Yes	Yes	Yes	Dec-19	No	PR	Jun-20	No	Sept-20
P053	1953	66	F	2	Unknown	Unmethylated	No			2	Jan-21	No	No	No	Jan-21	No	SD	Jun-21	No	Aug-21
P054	1966	62	F	1	Unmutated	Unknown	Yes	Jun-19	Partial	9	Aug-20	No	No	No	Nov-20	Yes	SD	Jun-21	Lomustina	Nov-21
P055	1955	63	F	1	Unmutated	Methylated	Yes	Jul-19	Complete	3	Feb-20	No	No	No	Feb-20	No	PR	Aug-20	No	Oct-20
P056	1955	64	M	1	Unknown	Unknown	Yes	Na	Partial	NA	Feb-20	No	No	No	Feb-20	No	PD	Aug-20	No	Sept-20

ECOG PS, Eastern Cooperative Oncology Group performance status; F, female; IDH, isocitrate dehydrojanase; M, male; MGMT, methylated methylguanine-DNA-methyltransferase; TMZ, temozolamide; CCS, corticosteroids; PR, partial response; SD, stable disease; PD, progressive disease; NA, not available.

RESORCE trial). All grade thrombocytopenia was reported by 13% of the cohort, with 5 grade 2 AEs and 2 grade 3 AEs, a result slightly more favorable than that of REGOMA trial, with 20% of grade 1-2 and 2% (1 patient) grade 3 thrombocytopenia and similar to the subsequent analysis by Lombardi *et al* (28).

AST elevation and hyperbilirubinemia were also among the most common AEs, with 11% manifesting AST elevation and 7% increase in bilirubinemia, similar to what was expected based on prior studies (21,34).

As already exposed, one of our main limitations is the retrospective nature of our study, determining a higher risk of incomplete data, information and recall bias, and the small population. However, our results are fairly superimposable to those of the available literature. This helps generating a framework in which regorafenib is a valid approach even in elderly patients due to both survival rates and toxicity profile being similar to those of a younger population. In any case, more phase 3 trials are needed to unravel the question of whether regorafenib is definitely superior to lomustine and define the best strategy at recurrence. An observational prospective study (REGOMA-Oss, [NCT04810182]) is already ongoing and will analyze the role of regorafenib in recurrent GBM in real world patients.

Unfortunately, predictive biomarkers of response to regorafenib are not yet available. In a recent study by Santangelo *et al* (35) based on patients from REGOMA trial, a group of 5 RNA biomarkers (HIF1a and CDKN1A mRNA, miR-93-5p, miR-3607-3p and miR301a-3p) identified a favorable subgroup of patients. These findings, given the relatively small population and the study design, must be validated in larger and in prospective trials (35).

Nevertheless, new studies are already exploring other strategies for regorafenib. GBM AGILE trial an international, seamless Phase II/III response adaptive randomization platform trial designed to evaluate multiple therapies, with regorafenib being used both at first diagnosis after concomitant CRT with temozolomide or at first recurrence. A phase II trial is evaluating regorafenib use in bevacizumab refractory high-grade gliomas (not only GBM but also gliosarcoma, small cell glioblastoma etc. can be included) [NCT04051606], while another phase II basket trial is investigating the association of regorafenib and nivolumab in several tumor types [NCT04704154].

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MF, FC and RA conceived the study. VF developed the methodology. VF, MP, SF, MCat, MCar, AB, IDG, AA SISF, TS, DS, MB, MCo, RP performed data analysis. MF, MP, VF,TS, DS, MB, MCo, RP, FC and RA performed data acquisition, analysis and interpretation. MCar, AV, IDG, AA, SISF, TS, DS, MB, MCo and RP provided resources. MF, MP, VF, IDG, AA, SISF and RA curated data. MF, MP, SF and MCat wrote the original draft. MF, TS, DS, MB, MCo, RP and FC reviewed and edited the manuscript. FC and RA supervised the study. FC and RA were involved in project administration. MF and RA confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study did not require ethical approval. Ethical review and approval were waived for this study due to the retrospective nature. The requirement for patient consent to participate was waived due to the retrospective nature of the study.

Patient consent for publication

The requirement for patient consent for publication was waived due to the retrospective nature of the study.

Competing interests

MF: Advisory boards for MSD and Merck Serono. All other authors declare that they have no competing interests.

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