Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): a multicentre, open-label, randomised, controlled, phase 2 trial

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See Comment page 10

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Summary

Background Glioblastoma is a highly vascularised tumour and there are few treatment options after disease recurrence. Regorafenib is an oral multikinase inhibitor of angiogenic, stromal, and oncogenic receptor tyrosine kinases. We aimed to assess the efficacy and safety of regorafenib in the treatment of recurrent glioblastoma.

Methods REGOMA is a randomised, multicentre, open-label phase 2 trial done in ten centres in Italy. Eligible patients (aged ≥18 years) with histologically confirmed glioblastoma, Eastern Cooperative Oncology Group performance status 0 or 1, and documented disease progression after surgery followed by radiotherapy and temozolomide chemoradiotherapy were randomly assigned (1:1) by a web-based system, stratified by centre and surgery at recurrence (yes *vs* no), to receive regorafenib 160 mg once daily for the first 3 weeks of each 4-week cycle or lomustine 110 mg/m² once every 6 weeks until disease progression, death, unacceptable toxicity, or consent withdrawal. The primary endpoint was overall survival in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT02926222, and is currently in follow-up.

Findings Between Nov 27, 2015, and Feb 23, 2017, 124 patients were screened and 119 eligible patients were randomly assigned to receive regorafenib (n=59) or lomustine (n=60). Median follow-up was 15·4 months (IQR 13·8–18·1). At the analysis cutoff date, 99 (83%) of 119 patients had died: 42 (71%) of 59 in the regorafenib group and 57 (95%) of 60 in the lomustine group. Overall survival was significantly improved in the regorafenib group compared with the lomustine group, with a median overall survival of 7·4 months (95% CI 5·8–12·0) in the regorafenib group and 5·6 months (4·7–7·3) in the lomustine group (hazard ratio 0·50, 95% CI 0·33–0·75; log-rank p=0·0009). Grade 3–4 treatment-related adverse events occurred in 33 (56%) of 59 patients treated with regorafenib and 24 (40%) of 60 with lomustine. The most frequent grade 3 or 4 adverse events related to regorafenib were hand–foot skin reaction, increased lipase, and blood bilirubin increased (in six [10%] of 59 patients each). In the lomustine group, the most common grade 3 or 4 adverse events were decreased platelet count (eight [13%] of 60 patients), decreased lymphocyte count (eight [13%]), and neutropenia (seven [12%]). No death was considered by the investigators to be drug related.

Interpretation REGOMA showed an encouraging overall survival benefit of regorafenib in recurrent glioblastoma. This drug might be a new potential treatment for these patients and should be investigated in an adequately powered phase 3 study.

Funding Veneto Institute of Oncology and Bayer Italy.

Introduction

Glioblastoma is the most common primary malignant brain tumour in adults.[1] The standard of care for newly diagnosed glioblastoma is a maximally safe resection followed by concomitant chemoradiotherapy and adjuvant chemotherapy with temozolomide.[2] Despite this approach, glioblastoma is associated with a poor median overall survival of less than 24 months and relapse is inevitable.[2,3] At recurrence, the standard of care is less well defined and efficacy is poor;[4] in this setting, a nitrosourea regimen is an option, and lomustine, a synthetic alkylating agent, has been widely used as a control in phase 2 and 3 trials in patients with recurrent glioblastoma.[5–9] Glioblastoma is one of the most vascularised tumours and is histologically characterised by the expression of VEGF and other proangiogenic cytokines that stimulate endothelial cell proliferation, migration, and survival.[10] Bevacizumab, an antibody that blocks VEGF-A ligand binding to VEGF receptor (VEGFR), is approved in the USA, but not in Europe, for the treatment of recurrent glioblastoma based on trials showing an improvement in progression-free survival compared with nitrosourea-based treatment.[11,12] However, bevacizumab alone or in combination with chemotherapy did not prolong overall survival as a first-line or second-line treatment for glioblastoma.[13] The

Research in context

Evidence before this study

We searched PubMed for articles published from Oct 1, 2012, to Jan 31, 2018, reporting on clinical trials in recurrent glioblastoma using the search terms "recurrent glioblastoma" and "treatment", with no language restrictions. The search retrieved 130 articles, of which 28 reported data from clinical studies (25 were non-comparative phase 2 trials and three were phase 3 trials) on treatment of recurrent glioblastoma, consisting of various combinations with bevacizumab or with drugs with innovative targets. The three phase 3 trials and most of the phase 2 trials were negative. Thus, evidence of efficacy for any treatment for patients with recurrent glioblastoma is scarce.

Added value of this study

Differently from other antiangiogenic drugs such as bevacizumab and cediranib, regorafenib is a multikinase inhibitor interfering not only with tumour angiogenesis, but also with other pathways involved in oncogenesis and the tumour microenvironment. To our knowledge, REGOMA is the first trial to assess regorafenib as monotherapy in patients with recurrent glioblastoma with overall survival as the primary endpoint. The results of REGOMA show that regorafenib significantly increased overall survival compared with lomustine in patients with recurrent glioblastoma. Improved outcomes were also shown for the secondary endpoints of progression-free survival and the proportion of patients achieving disease control.

Implications of all the available evidence

To our knowledge, REGOMA is the first comparative and randomised study to show an encouraging clinical benefit of regorafenib in patients with glioblastoma after failure of radiotherapy and temozolomide. These data further support the assessment of regorafenib in a phase 3 trial.

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European Organisation for the Research and Treatment of Cancer (EORTC) 26101 phase 3 trial[9] comparing lomustine plus bevacizumab or lomustine alone in the treatment of patients with recurrent glioblastoma showed no significant difference in overall survival (primary endpoint), despite an improvement in progression-free survival in the lomustine plus bevacizumab group. Similarly, two first-line phase 3 trials[14,15] found that the addition of bevacizumab to radiotherapy and temozolomide did not improve overall survival. One potential mechanism of glioblastoma resistance to bevacizumab activity derives from the development of VEGF-A-independent angio-genesis through ligand-mediated activation of alternative angiogenic receptors,[16] including some regorafenib targets.

Regorafenib is an orally available inhibitor of several kinases involved in tumour angiogenesis (VEGFR1–3 and TIE2), oncogenesis (*KIT*, *RET*, *RAF1*, and *BRAF* genes), the tumour microenvironment (platelet-derived growth factor receptor [PDGFR] and fibroblast growth factor receptor [FGFR]), and tumour immunity (colony-stimulating factor 1 receptor).[17–19]

Regorafenib is approved as monotherapy by the US Food and Drug Administration and European Medical Agency for the treatment of metastatic colorectal cancer, gastrointestinal stromal tumours, and hepatocellular carcinoma.[20–22] In a preclinical study,[18] regorafenib administered once orally at 10 mg/kg (standard rodent dose corresponding to a human dose of 160 mg) significantly decreased the extravasation of an MRI contrast agent (Gadomer 17) in the vasculature of a rat glioblastoma tumour xenograft, and was associated with therapeutic antitumour activity. In another preclinical study, regorafenib inhibited tumour growth in all patient-derived tumour xenografts, including gliomas; its antitumour activity was associated with decreased tumour vascularisation and inhibition of PDGFR pathways.[23] Moreover, in association with lapatinib, regorafenib showed activity against human glioblastoma cells.[24] Regorafenib was also evaluated in a phase 1 trial[25] in combination with cetuximab in patients with advanced cancer, including one patient with glioblastoma, with some evidence of clinical benefit.

Based on these characteristics and preclinical results, this randomised, comparative, multicentre phase 2 trial was designed to investigate the efficacy and safety of regorafenib in the treatment of patients with recurrent glioblastoma. The analysis of the primary endpoint was done on July 7, 2017, when 78 deaths had been reported, and presented at the European Society for Medical Oncology (ESMO) congress on Sept 8, 2017.[29] Overall survival was significantly improved in the regorafenib group (median 6·5 months, 95% CI 5·6–12·0) compared with the lomustine group (5·5 months, 4·7–8·0; HR 0·64, 80% CI 0·47–0·87; log-rank p=0·028). Here, we report the final results at the cutoff date of Dec 31, 2017.

Methods

Study design and participants

REGOMA is a randomised, multicentre, open-label phase 2 trial done in ten Italian clinical centres (three comprehensive cancer centres, three university hospitals, two neurological hospitals, and two general hospitals). The trial protocol is provided in the appendix (pp 10–95). Patients with histologically confirmed glioblastoma with unequivocal first progression after surgery followed by radiotherapy and temozolomide chemotherapy were eligible for inclusion. Additional inclusion criteria were age at least 18 years; Eastern Cooperative Oncology Group (ECOG) performance status score of 1 or lower (or Karnofsky performance score ≥70); disease progression on MRI as defined by Response Assessment in Neuro-Oncology (RANO) criteria[26] at least 12 weeks after completion of radiotherapy (unless the recurrence was

See Online for appendix

outside of the radiation field or had been histologically documented); at least one bi-dimensionally measurable target lesion with a diameter of at least 10 mm, visible on two or more axial slices 5 mm apart; on a stable or decreasing dose of steroids for 1 week before the baseline MRI scan; adequate bone marrow (haemoglobin >9·0 g/dL, white blood cells >3·0×10⁹/L, absolute neutrophil count >1500 per mm³ without transfusion or granulocyte colony stimulating factor, platelet count ≥100 000 per μL), liver (total bilirubin <1·5×upper limit of normal [ULN], alanine aminotransferase and aspartate aminotransferase <3×ULN), and renal function (serum creatinine <1·5×ULN and glomerular filtration rate ≥30 mL/min per 1·73 m²); serum lipase 1·5 times the ULN or lower, and prothrombin time–international normalised ratio less than 1·5 times the ULN. Local assessment of O-6-methylguanine-DNA methyltransferase (*MGMT*) methylation status on tumoural tissue at first surgery was required. Patients undergoing surgery for recurrence were eligible only if they had a histological confirmation of glioblastoma recurrence. Patients who had had surgery were eligible only if they had recovered fully before inclusion in the trial and could not start treatment until 4 weeks after surgery.

Exclusion criteria included previous chemotherapy for recurrent disease; previous treatment with regorafenib or any other VEGFR-targeting kinase inhibitor; treatment with temozolomide within the previous 4 weeks; recurrent disease located outside of the brain; uncontrolled hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg) despite optimal medical management; myocardial infarction less than 6 months before the start of study treatment; arterial thrombotic or embolic events, such as cerebrovascular accident (including transient ischaemic attacks) or pulmonary embolism within 6 months before the start of study treatment; active or chronic hepatitis B or C virus infection requiring treatment with antiviral therapy; and use of strong cytochrome P3A4 (CYP3A4) inhibitors or inducers (appendix pp 62–64).

All participating centres obtained written approval for the study from their local authorities and ethics committees. All patients signed an informed consent form approved by the ethics committee of the enrolling institution according to national regulations. The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Central data management, database development, statistical analysis, site monitoring, safety management, and trial management were done by the Clinical Trial Unit of the Veneto Institute of Oncology (Padova, Italy).

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive regorafenib or lomustine by a web-based system, stratified in block sizes of four by centre and surgery at recurrence (yes *vs* no).[27] In the original version of the protocol, randomisation had to be done using a minimisation method over five stratification factors: ECOG performance status (0 *vs* 1), *MGMT* methylation status at first surgery (methylated vs unmethylated), centre, time to first progression (before *vs* after completion of six cycles of temozolomide maintenance therapy), and previous use of bevacizumab and surgery at recurrence (yes *vs* no). Before authorising the study, the Italian competent authority (AIFA) asked to reduce the number of stratification factors on March 26, 2015. On April 1, 2015, an amendment using a stratified block randomisation scheme with two stratification factors, centre and surgery at recurrence (yes *vs* no), was implemented before starting patient recruitment. Neither investigators nor patients were masked to treatment allocation.

Procedures

Patients were randomly assigned to receive regorafenib 160 mg (given as four 40 mg tablets) orally once daily for the first 3 weeks of each 4-week cycle or lomustine 110 mg/m² (in 40 mg capsules, up to a maximum dose of 200 mg) orally on day 1 of every 6-week cycle until disease progression, death, unacceptable toxicity, or consent withdrawal. Prespecified dose modifications were planned in the protocol to manage toxicity (appendix pp 1–5); patients who required interruptions and dose reductions of regorafenib (to 120 mg, then 80 mg) could re-escalate the dose at the discretion of the investigator once the toxicity resolved to baseline levels. A second occurrence of an adverse event with a severity of grade 3 required a permanent reduction of dose level. A grade 4 adverse event required dose interruption until the severity was reduced to grade 2, with a subsequent permanent dose reduction of one dose level. Dose reductions leading to a daily dose below 80 mg were not permitted. Treatment was discontinued if the toxicity did not recover after a 4-week interruption.

Serum chemistry and haematological parameters were assessed weekly and every 2 weeks, respectively, for the first two cycles and then every month for the patients in the regorafenib group, and every 3 weeks for patients in the lomustine group. This different assessment in the two groups was planned to identify early any possible adverse events in the experimental group.

Radiological assessment was done by gadolinium brain MRI every 8 weeks (or within 1 week either side of this timepoint) from first drug administration until disease progression. Response was evaluated by the local investigator based on RANO criteria.

MGMT methylation status on tumoural tissue was assessed in a local laboratory for each participating centre by pyrosequencing or methylation-specific PCR. Isocitrate dehydrogenase (*IDH*) mutational status was also assessed in local laboratories by immunohistochemistry or by Sanger sequencing.

Safety assessments were done from the start of treatment until 30 days after the last dose of study drug

and comprised adverse events, laboratory abnormalities, vital signs, and electrocardiography. Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Health-related quality of life was measured using the EORTC QLQ-C30 and QLQ-BN20 questionnaires administered concurrently with MRI assessments (results will be reported separately). Tissue samples were collected for exploratory analyses to assess tissue biomarkers as potential predictors of response to regorafenib (results will be reported separately).

Outcomes

The primary endpoint was overall survival, defined as the time from randomisation until death from any cause. Secondary endpoints were progression-free survival (defined as the time from randomisation to tumour progression assessed by the local investigator according to RANO criteria or death), the proportion of patients achieving disease control (defined as stable disease, partial response, and complete response), the proportion of patients achieving an objective response (defined as partial and complete responses according to RANO criteria), health-related quality of life (the results of which will be reported separately), and safety (appendix p 40).

Statistical analysis

The sample size was calculated using a randomised phase 2 screening design,[28] with the aim to assess whether the experimental group (regorafenib) was more promising than the control group (lomustine) with respect to overall survival. Assuming a one-sided significance level of 0·20 and power of 80%, the study required 39 events and 112 eligible patients to detect a 42% reduction in the hazard ratio (HR) for death (one-sided log-rank test), which was the required threshold to warrant a future phase 3 trial. Overall survival and progression-free survival were analysed according to the intention-to-treat principle (including patients in the group to which they were assigned, whether or not they received the allocated treatment) and estimated using the Kaplan-Meier method. For the primary endpoint of overall survival, treatment groups were compared using a stratified log-rank test, and patients who were still alive at the date of analysis were censored. Patients without progression were censored at their final follow-up visit. Overall survival at 12 months and progression-free survival at 6 months are reported with 95% CIs calculated according to Greenwood's method. HRs with 95% CIs, were calculated according to the Wald method and using a Cox model. Fisher's exact test was used to compare the proportion of patients achieving disease control and the proportion of patients achieving an objective response between the treatment groups in the intention-to-treat population.

Adverse events and laboratory abnormalities were reported by treatment group, category, and worst grade experienced by the patient. Patients who received at least one dose of treatment under study were included in the safety analysis and toxicities were analysed according to

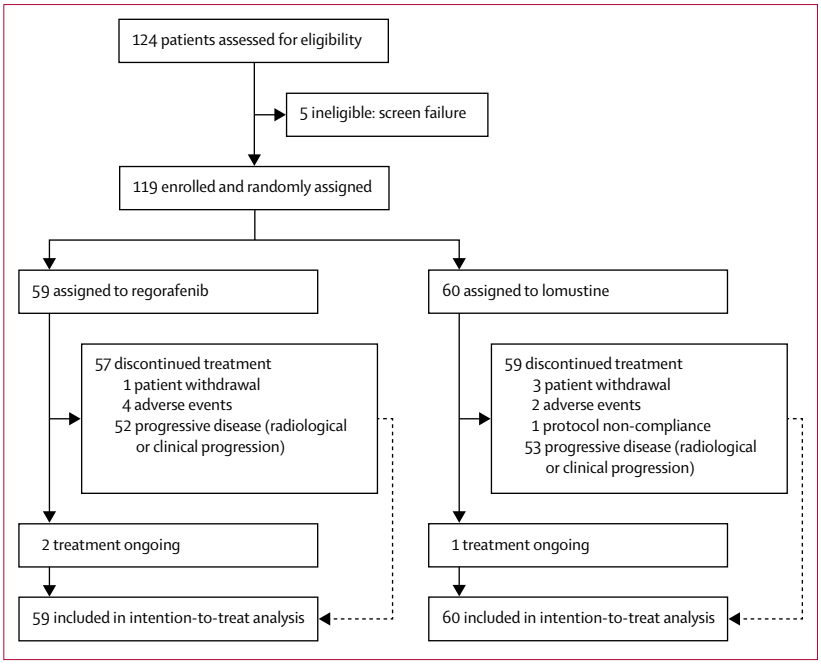

Figure 1: **Trial profile**

	Regorafenib group (n=59)	Lomustine group (n=60)
Age (years)	54·8 (46·8–61·3)	58·9 (51·8–65·2)
Sex		
Male	41 (69%)	43 (72%)
Female	18 (31%)	17 (28%)
ECOG performance status		
0	27 (46%)	28 (47%)
1	32 (54%)	32 (53%)
Surgery at the time of recurrence	13 (22%)	14 (23%)
Corticosteroid use	31 (53%)	37 (62%)
Median time since last radiotherapy (months)	9·6 (5·9–16·8)	8·3 (6·1–11·4)
IDH status		
Unmutated	42/44 (95%)	38/38 (100%)
Mutated	2/44 (5%)	0/38
Unknown	15	22
MGMT status		
Methylated	29/59 (49%)	27/59 (46%)
Unmethylated	30/59 (51%)	32/59 (54%)
Unknown	0	1

Data are median (IQR), n (%), or n/N (%). ECOG=Eastern Cooperative Oncology Group. *IDH*=isocitrate dehydrogenase. *MGMT*=O6-methylguanine-DNA-methyltransferase.

Table 1: **Demographics and baseline characteristics, and *MGMT* promoter gene methylation and *IDH* mutation status at initial diagnosis**

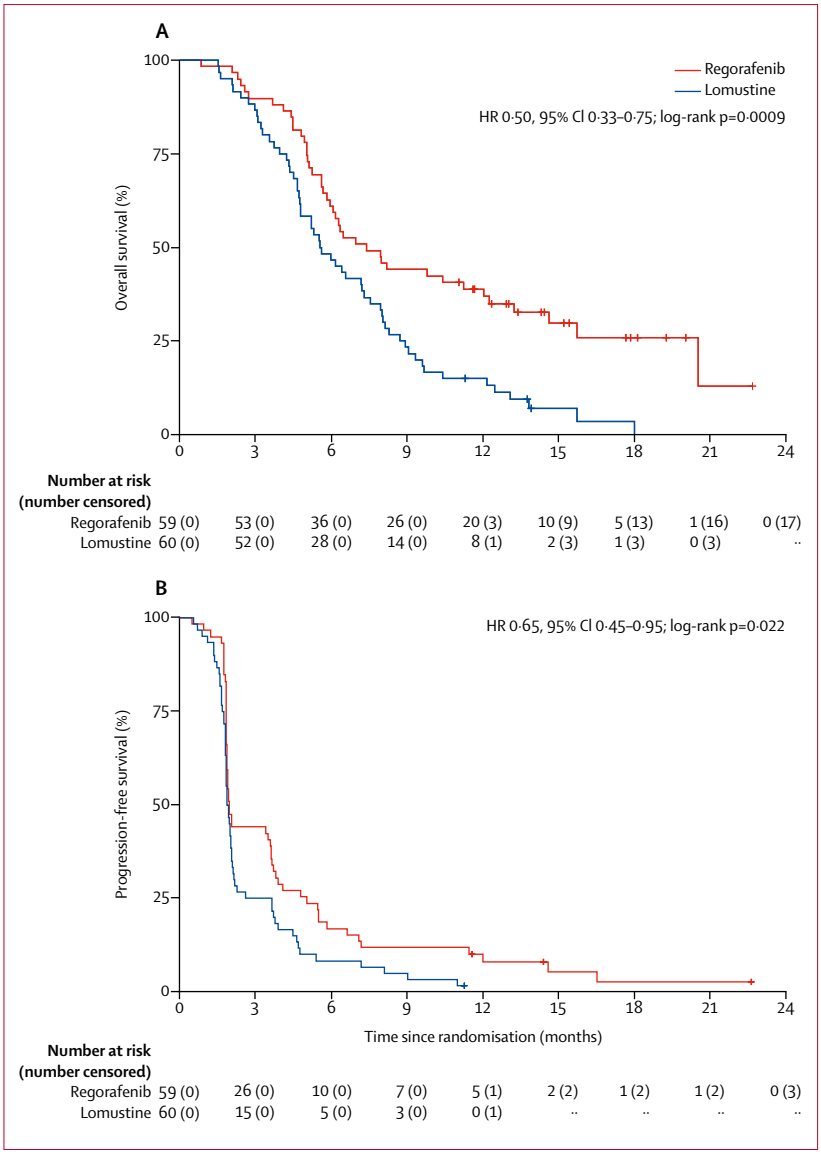

Figure 2: **Kaplan-Meier plots for overall survival (A) and progression-free survival (B)**
HR=hazard ratio.

the actual treatment received. Statistical analyses were done with SAS (version 9.4).

The trial was not overseen by a data monitoring committee. It is registered with the EU Clinical Trials Register database, number 2014-003722-41, and with ClinicalTrials.gov, number NCT02926222.

Role of the funding source

Veneto Institute of Oncology was the sponsor of this study. Bayer Italy provided partial financial support and provided regorafenib free of charge for all patients randomly assigned to the regorafenib group. Bayer Italy had no role in study design, data collection, interpretation, or analysis. Bayer Italy provided editorial assistance and had the right to review the report before publication. GLDS, GM, and VZ had full access to all the raw data, and the corresponding author (VZ) had final responsibility for the decision to submit for publication.

Results

Between Nov 27, 2015, and Feb 23, 2017, 124 patients were screened and 119 eligible patients were randomly assigned: 59 to regorafenib and 60 to lomustine (figure 1). Three centres enrolled three patients per centre and the remaining centres enrolled more than three patients (appendix p 6). Most baseline characteristics were similar between the two treatment groups (table 1; appendix p 7). Median time from last radiotherapy to randomisation was 9·6 months (IQR 5·9–16·8) in the regorafenib group versus 8·3 months (6·1–11·4) in the lomustine group. Patients in the regorafenib group were younger than those in the lomustine group (median age 54·8 years *vs* 58·9 years, respectively), had less corticosteroid use at baseline (53% *vs* 62%), had a higher frequency of *MGMT* methylation at diagnosis (49% *vs* 46%), and had a longer median time between diagnosis and first recurrence (10·7 months *vs* 9·8 months). One patient treated with lomustine had an unclear *MGMT* methylation status assessment according to local analysis and was classified as unknown. *IDH* mutational data were available for 44 of 59 patients in the regorafenib group and 38 of 60 in the lomustine group; among these, an *IDH1* mutation was identified in two patients treated with regorafenib. No *IDH2* mutations were identified in any patient.

The mean and median treatment durations (including interruptions and time off drug) were 16·1 weeks (SD 15·6) and 8·1 weeks (IQR 7·0–18·9) in the regorafenib group and 10·9 weeks (9·0) and 9·1 weeks (6·0–10·6) in the lomustine group, respectively. The mean daily dose of regorafenib was 149 mg (SD 17) and patients received a mean of 88% (16) of the planned dose. Patients treated with lomustine received a mean of 94% (SD 13) of the planned dose and a mean cycle dose of 168 mg (30).

At the analysis cutoff date of Dec 31, 2017, median follow-up was 15·4 months (IQR 13·8–18·1). 99 (83%) of 119 patients had died: 42 (71%) of 59 in the regorafenib group and 57 (95%) of 60 in the lomustine group. All but one death were due to disease progression; one death in the regorafenib group was due to non-treatment-related sepsis. 116 of 119 randomly assigned patients had discontinued treatment at analysis cutoff (figure 1). The most common reason for treatment discontinuation was disease progression in both groups (figure 1). Consent withdrawal was the reason for drug discontinuation in three patients (5%) receiving lomustine versus one (2%) receiving regorafenib.

Overall survival was significantly improved in the regorafenib group compared with the lomustine group. Median overall survival was 5·6 months (95% CI 4·7–7·3) with lomustine versus 7·4 months (5·8–12·0) with regorafenib (HR 0·50, 95% CI 0·33–0·75; log-rank p=0·0009; figure 2A). Overall survival at 12 months was

38·9% (95% CI 26·6–51·0) in the regorafenib group and 15·0% (7·4–25·1) in the lomustine group (table 2).

At the analysis cutoff date, 115 patients had disease progression or died: 56 (95%) of 59 in the regorafenib group and 59 (98%) of 60 in the lomustine group. Progression-free survival was longer in the regorafenib group than in the lomustine group (median progression-free survival 2·0 months [95% CI 1·9–3·6] in the regorafenib group *vs* 1·9 months [1·8–2·1] in the lomustine group; HR 0·65, 95% CI 0·45–0·95; log-rank p=0·022; figure 2B). Progression-free survival at 6 months was 16·9% (95% CI 8·7–27·5) in the regorafenib group and 8·3% (3·1–17·0) in the lomustine group.

All patients in the regorafenib group were assessed for overall response, whereas in the lomustine group, response was not assessed in three patients because they stopped treatment before the first assessment (one because of an adverse event and two withdrew consent), but these were included in the intention-to-treat population. One (2%) of 59 patients in the regorafenib group and one (2%) of 60 in the lomustine group had a complete response by RANO criteria as assessed by local investigators, whereas two patients (3%) in the regorafenib group and one (2%) in the lomustine group had a partial response, resulting in three (5%) of 59 patients in the regorafenib group and two (3%) of 60 patients in the lomustine group achieving an overall response (table 2). Most patients treated with regorafenib achieved stable disease as their best response (23 [39%] of 59 *vs* 10 [17%] of 60 for lomustine). 26 (44%) of 59 patients in the regorafenib group versus 12 (20%) of 60 in the lomustine group achieved disease control (Fisher's exact test p=0·0059).

A post-hoc exploratory analysis of overall survival by patient subgroups is shown in figure 3. In a post-hoc analysis, overall survival was longer in the regorafenib group than in the lomustine group regardless of *MGMT* methylation status (appendix p 9).

57 patients developed at least one treatment-related grade 3–4 adverse event during the REGOMA trial (table 3; appendix p 8): 33 (56%) of 59 patients treated with regorafenib and 24 (40%) of 60 with lomustine. In the regorafenib group, the most frequent grade 3 or 4 adverse events were hand–foot skin reaction, increased lipase, and increased blood bilirubin (in six [10%] of 59 patients each). In the lomustine group, the most common grade 3 or 4 adverse events were decreased platelet count (eight [13%] of 60 patients), decreased lymphocyte count (eight [13%]), and neutropenia (seven [12%]). Two cases of grade 1–2 drug-related infections were reported in the regorafenib group (one case classified as infections and infestations, other, and one as tooth infection). Serious adverse events occurred in 13 (22%) of 59 patients treated with regorafenib and ten (17%) of 60 patients treated with lomustine; most of these were neurological symptoms due to the disease under study or progressive disease, or both (eight of 59 patients treated with regorafenib and seven of 60 patients treated with lomustine). Five events were related to the study drug: in three (5%) of 59 patients treated with regorafenib (two gastrointestinal disorders and one increased blood bilirubin) and in two (3%) of 60 patients treated with lomustine (one pancytopenia and one decreased platelet count).

	Regorafenib group (n=59)	Lomustine group (n=60)	Hazard ratio (95% CI)
Overall survival			
Median (95% CI)	7·4 (5·8–12·0)	5·6 (4·7–7·3)	0·50 (0·33–0·75)
At 12 months (95% CI)	38·9% (26·6–51·0)	15·0% (7·4–25·1)	..
Progression-free survival			
Median (95% CI)	2·0 (1·9–3·6)	1·9 (1·8–2·1)	0·65 (0·45–0·95)
At 6 months (95% CI)	16·9% (8·7–27·5)	8·3% (3·1–17·0)	..
Overall responses according to RANO criteria			
Disease control	26 (44%)	12 (20%)	..
Objective response	3 (5%)	2 (3%)	..
Complete response	1 (2%)	1 (2%)	..
Partial response	2 (3%)	1 (2%)	..
Stable disease	23 (39%)	10 (17%)	..
Progressive disease	33 (56%)	45 (75%)	..
Response not assessed	0	3 (5%)	..

Data are n (%), unless otherwise specified. RANO=Response Assessment in Neuro-Oncology.

Table 2: **Survival and response endpoints**

Drug-related adverse events led to dose reductions in ten (17%) of 59 patients treated with regorafenib and 11 (18%) of 60 patients treated with lomustine. 27 (46%) of 59 patients in the regorafenib group had at least one drug-related treatment interruption or delay compared with 12 (20%) of 60 patients in the lomustine group. Adverse events led to permanent treatment discontinuation in four (7%) of 59 patients treated with regorafenib (one intestinal perforation, one increased lipase, one seizure, and one abdominal abscess with splenic infarct) and in two (3%) of 60 patients with lomustine (one pulmonary embolism and one episode of mental confusion and disorientation). No death was considered by the investigators to be related to study drugs.

Regarding salvage therapies at disease progression, 38 (64%) of 59 patients treated with regorafenib received a third-line treatment option, mainly fotemustine, a third-generation nitrosourea (30 [79%] of 38 patients). One (3%) of 38 patients received lomustine plus procarbazine, one patient was treated with bevacizumab alone, and another patient with bevacizumab plus fotemustine after regorafenib treatment. In the lomustine group, 26 (43%) of 60 patients received a third-line treatment. Among these, 13 (50%) patients were treated with fotemustine, four (15%) received bevacizumab, and two (8%) received bevacizumab plus fotemustine. No patient in the lomustine group received regorafenib after disease progression.

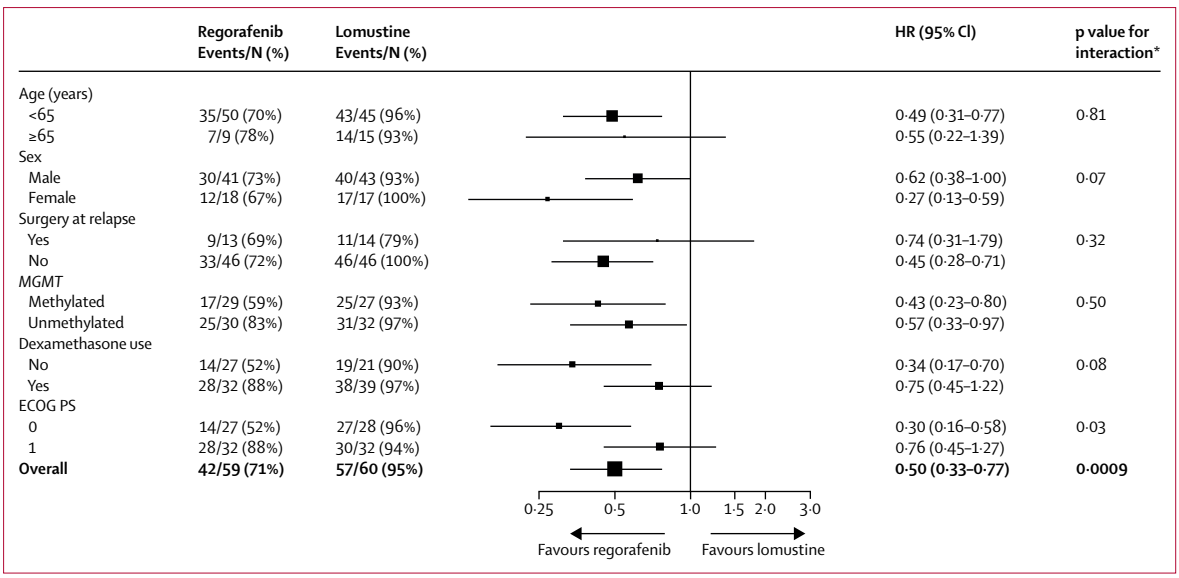

***Figure 3*: Post-hoc subgroup analyses**
ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. *Unadjusted for multiplicity.

	Regorafenib group (n=59)			Lomustine group (n=60)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Laboratory abnormalities						
Blood bilirubin increased	14 (24%)	6 (10%)	0	2 (3%)	0	0
Platelet count decreased	12 (20%)	1 (2%)	0	18 (30%)	8 (13%)	0
Hypothyroidism	11 (19%)	0	0	0	0	0
Lipase increased	7 (12%)	6 (10%)	0	0	1 (2%)	0
Hypertransaminasaemia	6 (10%)	1 (2%)	1 (2%)	1 (2%)	2 (3%)	0
Serum amylase increased	5 (8%)	2 (3%)	0	1 (2%)	0	0
Anaemia	4 (7%)	0	0	6 (10%)	0	0
Lymphocyte count decreased	2 (3%)	3 (5%)	0	2 (3%)	8 (13%)	0
Neutropenia	1 (2)	1 (2%)	0	4 (7%)	7 (12%)	0
Clinical adverse events						
Fatigue	14 (24%)	2 (3%)	0	9 (15%)	1 (2%)	0
Hand–foot skin reaction	13 (22%)	6 (10%)	0	0	0	0
Hypertension	13 (22%)	1 (2%)	0	0	0	0
Diarrhoea	9 (15%)	1 (2%)	0	1 (2%)	0	0
Rash or desquamation	7 (12%)	2 (3%)	0	0	0	0
Constipation	4 (7%)	2 (3%)	0	0	0	0

Events listed are treatment-emergent adverse events occurring in at least 10% of patients in either treatment group. The complete list is shown in the appendix (p 8).

***Table 3*: Drug-related treatment-emergent adverse events**

Discussion

The REGOMA study showed an overall survival benefit of a multikinase inhibitor that interferes with the tumour vasculature and growth. The 12-month overall survival in the regorafenib group was twice that reported in the lomustine group and, the statistically significant HR of 0·50 suggests that patients receiving regorafenib had a substantial and clinically meaningful reduction in the risk of death compared with those treated with lomustine.

To our knowledge, REGOMA is the first study to assess the role of regorafenib as a monotherapy in patients with relapsed glioblastoma who had received treatment with first-line chemoradiation,[30] with overall survival as the primary endpoint. Despite a strong rationale for using antiangiogenic drugs in glioblastoma, previous phase 3 trials evaluating bevacizumab (a VEGF inhibitor),[9] cediranib (a VEGFR tyrosine kinase inhibitor),[6] and enzastaurin (an oral serine/threonine kinase inhibitor)[7] did not show improvements in overall survival in patients with recurrent glioblastoma. A 2017 meta-analysis of phase 2 and 3 trials[13] evaluating the effectiveness of antiangiogenic drugs in the first-line setting and in patients with recurrent glioblastoma showed no improvement in overall survival, with a pooled HR of 1·00 (95% CI 0·92–1·10; p=0·9). The BELOB trial[8] was a randomised, controlled, but non-comparative study assessing the role of bevacizumab in the treatment of recurrent disease. The primary endpoint was overall survival at 9 months and the trial showed a possible benefit of the combination of bevacizumab plus lomustine compared with bevacizumab or lomustine alone. The recently reported final data from the EORTC 26101 phase 3 trial[9] did not show an overall survival benefit of bevacizumab added to lomustine compared with lomustine alone, even though locally assessed progression-free survival, according to RANO criteria, was better in the combination group (4·2 months [95% CI 3·7–4·3] *vs* 1·5 months [1·2–2·5]; HR 0·49, 95% CI 0·39–0·61; p<0·001). Overall, the addition of bevacizumab to lomustine did not provide a survival advantage, with a median overall survival of 9·1 months (95% CI 8·1–10·1) in the combination group and 8·6 months (7·6–10·4) in

the monotherapy group (HR 0·95, 95% CI 0·74–1·21; p=0·65).

Our trial with a mature follow-up showed that regorafenib led to a statistically significant improvement in both progression-free and overall survival. Similarly to the EORTC 26101 trial,[9] we used RANO criteria to assess response to treatment. In the EORTC 26101 trial,[9] median progression-free survival was 2·7 months longer in the combination group than in the lomustine group, whereas in our study we noted a similar median progression-free survival in the two groups (2·0 months in the regorafenib group and 1·9 months in the lomustine group). Despite this small difference, patients treated with regorafenib had a significantly longer progression-free survival. Moreover, at 6 months from randomisation, the percentage of patients treated with regorafenib who were progression free was two times higher than with lomustine. The higher percentage of patients having stable disease or an overall response to regorafenib probably led to the increase in progression-free survival and overall survival. Moreover, the percentage of patients alive at 12 months from randomisation was more than doubled with regorafenib versus lomustine. These results are relevant in a population with a very poor prognosis and an unmet clinical need.

MGMT methylation analyses were done locally in all 119 enrolled patients, and *MGMT* methylation status did not predict the efficacy of regorafenib: there was a significant overall survival benefit with regorafenib in patients with both methylated and unmethylated *MGMT*. Regorafenib was superior to lomustine in patients with methylated *MGMT*, despite various studies[31,32] showing that methylated *MGMT* might have a role in predicting longer survival in patients with recurrent glioblastoma treated with alkylating agents.

Assessment of *IDH* mutational status was done in 82 patients and among these, two patients treated with regorafenib had an *IDH1* mutation. No *IDH* mutation was identified in the lomustine group. Mutations in *IDH* are present in so-called secondary glioblastoma and are important prognostic factors for longer overall survival in patients with newly diagnosed glioblastoma; however, discordant results exist about their prognostic role in recurrent disease.[8,33]

Although we reported a statistically significant benefit of regorafenib, the median overall survival in both the lomustine and the experimental groups was lower than those reported in other recent randomised trials,[6–9] which reported a median overall survival of about 7–10 months for patients receiving lomustine as comparator. Similarly, the AVAREG trial,[32] another Italian phase 2, randomised and non-comparative study of fotemustine or bevacizumab in patients with recurrent glioblastoma, reported a median overall survival of 7·3 months with bevacizumab and 8·7 months with fotemustine. A likely explanation is that the high heterogeneity of glioblastoma led to different responses to treatment and survival; indeed, some studies reported a similar or even lower median overall survival to that reported in our study.[34,35] Another explanation could be that this trial might have enrolled less selected patients with recurrent glioblastoma compared with previous studies.

The safety profile of regorafenib in the REGOMA trial was as expected, consistent with previous clinical experience,[20,22] and manageable with no new safety signals. No deaths were attributed to adverse events associated with regorafenib, suggesting that a careful evaluation of patients treated with regorafenib for early onset of adverse events might enable better tolerability; for this reason, serum chemistry and haematological parameters were assessed weekly for the first two cycles in the regorafenib group. The most common grade 3 or 4 adverse events were hand–foot skin reaction, blood bilirubin, and increased lipase. The incidence of grade 3–4 hand–foot skin reaction was lower than that reported in the CORRECT trial (10% *vs* 17%).[20] This difference might be due to a lower exposure to previous cytotoxic drugs, better liver function, and a higher use of steroid in patients with relapsed glioblastoma in our study compared with those with relapsed metastatic colorectal cancer in the CORRECT trial. In our study, grade 3 drug-related hypertension was reported in one patient (2%) treated with regorafenib, whereas the previous phase 3 studies in hepatocellular carcinoma[22] reported grade 3 and 4 drug-related hypertension in 13% and 1% of cases, respectively. Moreover, in the CORRECT study,[20] 7% of patients reported grade 3 drug-related hypertension. However, the reason for the higher rate of grade 3–4 increased blood bilirubin reported in the REGOMA trial (10%) compared with the CORRECT[20] (6%) and RESOURCE[22] (2%) studies remains unclear, and such cross-trial comparison must be made with caution. In the EORTC 26101 trial,[9] patients treated with bevacizumab plus lomustine reported a lower rate of treatment-related grade 3–5 adverse events (39%) than those receiving regorafenib in the REGOMA study (56%), but among these 39%, five treatment-related deaths were described.

Although the occurrence of grades 3–4 drug-related adverse events in the regorafenib group of the REGOMA trial was higher than in the lomustine group, patients treated with regorafenib received a mean of 88% of the planned dose and the mean treatment duration was longer in the regorafenib group than in the lomustine group. Since regorafenib is metabolised by CYP3A4, patients on strong CYP3A4 inhibitors or inducers were not enrolled in the study. Indeed, strong CYP3A4 inhibitors can cause a higher plasma concentration of regorafenib. Conversely, some antiepileptic drugs, such as carbamazepine, phenytoin, and phenobarbital, are strong inducers of CYP3A4 and could decrease the efficacy of regorafenib owing to lower plasma concentration. Hence, their concomitant administration with regorafenib was not allowed.

A translational research programme associated with the REGOMA trial included evaluation of several in-situ

biomarkers in tumour sections. Biomarkers included the main vascular targets of regorafenib (ie, VEGFR, FGFR, TIE2, and PDGFR) and some metabolism-associated biomarkers; expression of c-KIT will also be evaluated in the context of these studies. Results of translational research will be published in a separate manuscript. Quality of life is another important outcome to be evaluated in these patients. It was measured using the EORTC QLQ-C30 and QLQ-BN20 questionnaires; these analyses are ongoing and results will be published subsequently.

A weakness of our study could be that, despite randomisation, patients receiving regorafenib might have a few more favourable prognostic factors; specifically, they were about 4 years younger, slightly more had *MGMT* methylation at diagnosis, fewer used steroids at baseline, and they had longer median time between diagnosis and first recurrence compared with patients in lomustine group. Another potential limitation of our study is the absence of an independent and central neuroradiology and histopathology review. This was not done because REGOMA is an academic study with finite financial support, but these central reviews will be mandatory in the next phase 3 study. However, all ten centres involved in REGOMA have substantial clinical experience and international relevance in neuro-oncology. Moreover, a strength of the REGOMA design was the primary endpoint of overall survival.

More patients in the regorafenib group received a third-line therapy (mostly fotemustine) compared with those in the lomustine group, which might have favoured the regorafenib group in terms of overall survival. However, after second progression, the clinical advantage of subsequent lines of chemotherapy is controversial and needs to be clarified.[36,37] Conversely, third-line bevacizumab was hypothesised to prolong overall survival[38] in respect of chemotherapy, and in the REGOMA study more patients were treated with bevacizumab after lomustine than after regorafenib.

In conclusion, this multicentre, randomised phase 2 trial showed encouraging results of regorafenib in patients with recurrent glioblastoma. A subsequent randomised phase 3 study is being planned.

Contributors

GL, GLDS, and VZ designed the study and prepared the protocol. GL, AAB, ME, RR, MFal, IL, APac, BD, FP, SR, LB, APam, MFar, RS, and VZ collected the data. GL acted as principal investigator and VZ was the REGOMA study coordinator. GLDS and GM did the statistical analysis. GLDS coordinated the data centre. GL, GLDS, and VZ wrote the paper. SI and MPG coordinated the translational research. All authors reviewed and approved the final version.

Declaration of interests

Veneto Institute of Oncology received a grant from Bayer to partially support the study. GL received personal fees from Bayer, outside the submitted work. GL, GLDS, and SI are co-inventors in a pending patent application: development of a biomarker predictive of response to regorafenib in glioblastoma patients (number: 102018000003449). BD reports personal fees and non-financial support from Bayer and Bristol-Myers Squibb; personal fees from IPSEN, EISAI, Lilly, MSD, and Merck; and non-financial support from Sanofi, outside the submitted work. VZ reports personal fees and an advisory role from Bristol-Myers Squibb; an advisory role and travel and accomodation expenses from Celgene; non-financial support, an advisory role, and travel and accommodation expenses from Merck; personal fees and non-financial support from Bayer and Roche; and personal fees from Pfizer, Janssen, Novartis, Astellas, and Servier, outside the submitted work. All other authors declare no competing interests.

Data sharing

Individual patient data are not publicly available since this was not foreseen by the study protocol. The study protocol is available in the appendix (pp 10–95).

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