Trials

STUDY PROTOCOL

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Regorafenib versus local standard of care in patients with grade 2–3 meningioma no longer eligible for loco-regional treatments: a phase II randomized controlled trial (the MIRAGE study)

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Abstract

Background Regorafenib is an oral multi-tyrosine kinase (RTK) inhibitor. It exhibits high selectivity for VEGFR1/2/3, while also inhibiting PDGFRβ, FGFR1, and oncogenic signaling cascades involving c-RAF/RAF1 and BRAF. These pathways are highly expressed in meningiomas, particularly in high-grade meningiomas.

Methods The MIRAGE trial (NCT06275919) is a multicenter, open-label, controlled, randomized phase 2 clinical trial evaluating grade 2/3 meningioma patients who have progressed following surgery and radiotherapy. A total of 94 participants are being randomized (1:1) to receive either regorafenib (160 mg orally for 3 weeks on, 1 week off) or local standard-of-care therapies (e.g., bevacizumab, hydroxyurea, somatostatin analogs). Major inclusion criteria include histological confirmation of grade 2 or grade 3 meningioma according to the WHO 2021 classification, radiologically documented progression according to RANO criteria with at least 1 measurable lesion (minimum 10 × 10 mm) on baseline MRI, ineligibility for further surgery and/or radiotherapy, and a WHO performance status of 0–1. The primary endpoint is 6-month progression-free survival (6m-PFS) and secondary endpoints include overall survival (OS), objective response rate (ORR), disease control rate (DCR), safety, and health-related quality of life. Exploratory analysis will also be performed. MIRAGE, initiated in September 2024, is an academic trial promoted by the Istituto Oncologico Veneto, IOV-IRCCS, and will recruit patients across 15 neuro-oncology centers in Italy with an estimated study duration of 18 months.

Discussion MIRAGE is a phase 2 trial designed to determine the role of regorafenib in prolonging the PFS of grade 2–3 meningioma patients ineligible for further surgery and/or radiotherapy.

Trial registration ClinicalTrials.gov NCT06275919. Registered before start of inclusion, 7 February 2024. EuCT no. 2024–510954-28.

Keywords Meningioma, MIRAGE, Regorafenib, Randomized controlled trial

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Background

Meningiomas are among the most common intracranial tumors, with an estimated incidence of 8 cases per 100,000 people per year at histopathology. Approximately 70–80% of cases are of benign histology and correspond to grade 1 according to the 2021 WHO classification, whereas up to 20–30% of cases show signs of increased malignancy at histology and correspond to grade 2–3 meningiomas [1]. The majority (90%) of meningiomas are located intracranially, but 10% are found in the spinal meninges [2].

Surgical resection is curative in 70–80% of cases. However, incomplete resection substantially raises the risk of recurrence. Therefore, radiotherapy or stereotactic radiosurgery should be considered in meningiomas that were not gross totally resected as well as in higher grade tumors. Radiotherapy is usually recommended for recurrent meningiomas after initial surgical resection and it is administered either as monotherapy or as adjuvant therapy after re-resection. The role of radiotherapy in the first-line treatment of atypical meningiomas will be clarified by the final results of the ROAM/EORTC 1308 trial. For grade 3 meningiomas, surgery followed by adjuvant radiotherapy is recommended and improves 5-year progression-free survival from 15 to 80% [3].

Most patients with recurrent disease do exhaust all surgical and radiotherapeutic options in their disease course and become candidates for systemic therapies. Efforts to identify systemic treatments have largely yielded limited success. Investigational agents such as hydroxyurea, temozolomide, irinotecan, interferon-alpha, somatostatin analogs, imatinib, and erlotinib have been evaluated mostly in small and uncontrolled studies and patient series and seem largely ineffective with controversial results [4]. In the only randomized study (EORTC 1320), grade 2–3 meningioma patients relapsing after surgery and radiotherapy were randomized to receive trabectedin (experimental arm) or local standard of care (LSC) with no statistical difference between the two arms in terms of both PFS and OS. In this study, 90 patients were randomized (61 in trabectedin arm and 29 in LSC); median PFS was 4.17 months in the LSC and 2.43 months in the trabectedin arm ($p=0.2$) with a PFS-6 rate of 29.1% and 21.1%, respectively. Median OS was 10.6 months in the LSC and 11.37 months in the trabectedin arm ($p=0.94$). In the LSC arm, bevacizumab and hydroxyurea were the most commonly chosen drugs. With hydroxyurea therapy, the authors observed a median PFS of 2.4 months, a PFS-6 rate of 8.8%, a median OS of 7.4 months, and an OS-6 rate of 55.9%. With bevacizumab treatment, the authors observed a median PFS of 6.0 months, a PFS-6 rate of 44.4%, a median OS of 13.5 months, and an OS-6 rate of 88.9% [5].

Small trials and case series suggest clinical relevant activity of several vascular endothelial growth factor (VEGF) inhibitors such as sunitinib, bevacizumab, and vatalanib reporting a 6m-PFS rate of 42–64%. Indeed, VEGF and VEGF receptors (VEGFR) are regularly overexpressed in meningiomas and can correlate with outcome [6, 7]. Sunitinib is an orally administered tyrosine kinase inhibitor targeting VEGFR, PDGFR, and KIT. In a prior study by Kaley et al., 36 patients with recurrent grade 2–3 meningiomas were treated with sunitinib reporting PFS-6 of 42% and so, meeting the primary endpoint. Median PFS was 5.2 months and median overall survival was 24.6 months [8].

Regorafenib shares with sunitinib a similar mechanism of action. It inhibits angiogenic receptor tyrosine kinases (RTKs) and is highly selective for VEGFR1/2/3; moreover, regorafenib inhibits PDGFRB, FGFR1, and oncogenic intracellular signaling cascades involving c-RAF/RAF1 and BRAF highly expressed in meningiomas. The study drug, regorafenib, is supplied free of charge by Bayer SpA. MIRAGE is an investigator-initiated clinical trial. Bayer SpA holds no influence over study design, data collection, analysis, or publication decisions, ensuring the trial's scientific independence.

Here, we summarize the clinical trial design of this ongoing study with first site activation achieved in October 2024.

Study design

MIRAGE is a multicenter, open-label, controlled, randomized, superiority phase 2 clinical trial in patients with grade 2–3 recurrent meningioma who are no longer eligible for loco-regional treatments. Figure 1 summarizes the trial design. Of note, the information provided reflects the protocol version 1.1 approved on 5 June 2024.

Trial population

The detailed eligibility criteria are reported in Table 1. Main inclusion ones include histological diagnosis of grade 2 or grade 3 meningioma according to the WHO 2021 classification, radiologically documented progression (estimated planar growth > 25% measured in two dimensional tumor area—within the prior 12 months or a new lesion development, time from the last radiotherapy of at least 24 weeks), ineligibility for further surgery and/or radiotherapy, at least 1 measurable lesion (minimum 10 × 10 mm) on baseline MRI, absence of extracranial disease, and a WHO performance status of 0–1. Participants will receive comprehensive details regarding the study design, objectives, and requirements from certified investigators who hold Good Clinical Practice (GCP) certification. Investigators will ensure that

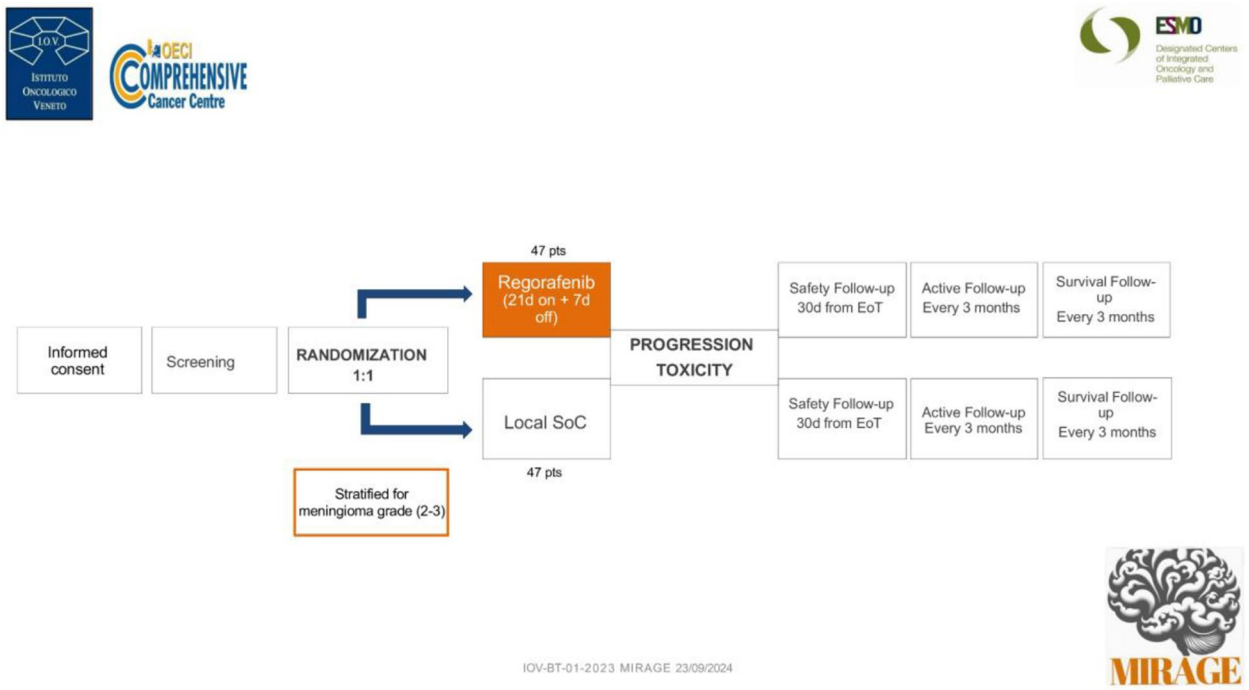

Fig. 1 Study scheme of the MIRAGE trial

patients fully understand their involvement, including the importance of follow-up visits. The significance of adherence to scheduled assessments will be emphasized to maintain data integrity and enhance study reliability.

Study endpoints

The objectives and the endpoints of the MIRAGE trial are reported in Table 2. Briefly, the primary endpoint is represented by 6m-PFS in the intent-to-treat (ITT) population. Secondary objectives are OS, disease control rate (DCR), objective response rate (ORR), safety, and health-related quality of life. An exploratory analysis, as described below, will also be performed.

6m-PFS is defined as the proportion of patients who remained alive and progression-free at 6 months. OS is defined as the time from randomization to death due to any cause. Patients alive at the time of the analysis will be censored at the date of last assessment.

PFS, DCR, and ORR will be radiologically assessed by performing a cranial MRI every 12 weeks. MRI will be evaluated according to Response Assessment in Neuro-Oncology (RANO) criteria interpretation by the local investigators and subsequently centrally reviewed to ensure data consistency.

Toxicity during treatment will be graded according to CTCAE version 5.0. Health-related quality of life will be assessed at the baseline and concurrently to every brain MRI assessment using EORTC Quality of Life Questionnaire (QLQ)-C30 and QLQ-BN20. Compliance will be calculated as the number of acceptable forms received out of the number expected at each assessment point, and differences between the two treatment arms will be tested using the Fisher exact test.

Exploratory analyses of tissue will be performed to investigate possible prognostic and predictive biomarkers: genetic alterations of genes associated with prognosis in meningioma patients and of potential predictive value, such as NF2, will be investigated by NGS using the TSO500 DNA/RNA panel, on Illumina Novaseq sequencer. Tumor DNA from FFPE sections will be required for these analyses. Analysis of germinal DNA is not planned. Methylome will be performed by Illumina epic 850k. Additional markers will include analysis of phosphorylated (Ser79) acetyl-CoA carboxylase (pACC) expression, which in a previous study showed predictive value in glioblastoma patients treated with regorafenib [9]. pACC protein expression will be assessed in FFPE tumor sections by IHC followed by digital pathology analysis, according to an established protocol. Finally, RNA will be obtained from FFPE tumor sections and subjected to RNAseq analysis in order to interrogate the presence of a signature previously associated by our team to response to regorafenib [10], as well as novel metabolism-related signatures which could correlate with drug response.

Table 1 Inclusion and exclusion criteria of the MIRAGE trial

Inclusion Criteria	Exclusion Criteria
Histological diagnosis of grade 2 or 3 meningioma according to the WHO 2021 classification.	Prior antineoplastic therapy for meningioma.
Radiologically documented progression (estimated planar growth >15% measured in two-dimensional tumor area within the prior 6 months or development of a new lesion).	Previous treatment with Regorafenib or other VEGFR-targeting kinase inhibitors.
Ineligible for further surgery and/or radiotherapy.	Extracranial disease.
At least one measurable lesion (minimum 10 x 10 mm) on baseline magnetic resonance imaging (MRI).	Uncontrolled hypertension despite optimal medical management.
WHO Performance Status 0-1.	Myocardial infarction less than 6 months before the start of study treatment.
Male or female aged ≥ 18 years.	Arterial thrombotic or embolic events within 6 months before the start of study treatment.
Availability of paraffin-embedded tumor tissue.	Active or chronic hepatitis B or C virus infection requiring antiviral therapy.
Dosage of dexamethasone or equivalent steroids ≤ 4 mg/day within 7 days prior to randomization.	Use of strong cytochrome P3A4 inhibitors or inducers.
Stable or decreasing steroid dosage for at least 7 days prior to randomization.	Use of strong UGT1A9 inhibitors (e.g., mefenamic acid, diflunisal, or niflumic acid).
Adequate cardiac, hepatic, renal, and hematological function.	Recurrent disease located in the brainstem or spinal cord.

WHO World Health Organisation, *VEGFR* Vascular Endotelial Growth Factor Receptor, *MRI* Magnetic Resonance Imaging

Table 2 Objectives and endpoints of the MIRAGE trial

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
Evaluate the role of Regorafenib in prolonging progression-free survival (PFS) in patients with grade 2 or 3 meningioma.	Progression-free survival (PFS): Time from randomization to disease progression or death, whichever occurs first.
Secondary Objectives	**Secondary Endpoints**
1. Assess overall survival (OS).	Overall survival (OS): Time from randomization to death from any cause.
2. Evaluate objective response rate (ORR).	Objective response rate (ORR): Proportion of patients achieving complete response (CR) or partial response (PR).
3. Determine disease control rate (DCR).	Disease control rate (DCR): Proportion of patients achieving CR, PR, or stable disease (SD).
4. Assess safety and tolerability.	Toxicity graded according to the NCI-CTCAE v.5.
5. Evaluate patient-reported quality of life (QoL).	Quality of life (QoL): Scores from EORTC QLQ-C30 and QLQ-BN20 questionnaires.
Exploratory Objectives	**Exploratory Endpoints**
1. Analyze antiangiogenic and metabolic biomarkers in tissue.	Identification of biomarkers predictive of tumor response to Regorafenib.
2. Investigate immunological characteristics and their impact on treatment response.	Analysis of myeloid cells and specific biomarkers at baseline.
3. Conduct radiomics analysis on baseline MRI to explore predictive characteristics for efficacy and toxicity.	Radiomics data associated with treatment outcomes.

NCI-CTCAE National Cancer Institute-Common Terminology Criteria for Adverse Events, *EORTC-QLQ* European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire

Table 3 Study calendar of the MIRAGE trial

Study Phase	Assessment/Procedure	Screening (Day -28 to 0)	Baseline (Day 0)	Every 2 weeks	Every 4 weeks	Every 9 weeks	End of Study
Eligibility	Informed consent	X					
	Inclusion/exclusion criteria	X					
Baseline	Medical history	X					
	Physical exam	X	X		X		X
	Laboratory tests	X	X		X		X
	Imaging (MRI, CT)	X				X	X
Intervention	Regorafenib administration		X	X			
Safety	Adverse events		X	X	X	X	X
Follow-up	QoL assessment				X	X	X
	Survival status						X

MRI Magnetic Resonance Imaging, *CT* Computed Tomography

Exploratory analyses of specific myeloid cells and biomarkers will be carried out to evaluate their prognostic and predictive value: a multiparametric flow cytometry analysis will be performed on blood at baseline. Cell levels of CD14+, CD14+/p-STAT3+, CD14+/PD-L1+, and CD15+cells and of 4 MDSC subsets will be evaluated. Arginase-1 (ARG1) quantity and activity will be determined in the plasma. These analyses are optional.

Further biomarkers will be added in the analysis, at protein, transcript, and miR levels, in case during the course of the clinical trial new reports in the scientific literature will indicate their role as prognostic or predictive biomarkers in the antiangiogenic therapy.

Finally, radiomics analysis will be performed to identify predictive factors of treatment. Semi-automatic segmentation of meningioma will be performed across different imaging sequences. To ensure the accuracy and validity of the results, lesions will be segmented by the consensus of two neuroradiologists. Radiomic features will be extracted from MRI data using the PyRadiomics and radiomic signature extraction following the Image Biomarker Standardization Initiative guidelines.

Table 3 summarizes study calendar before treatment start, during treatment, and during follow-up.

Statistical considerations

To test the assumption that 6-month PFS will be 20% in the control arm and 40% in the experimental arm based on the log-rank test, on a type I error equal to 5% one-sided and on a power equal to 85% corresponding to a hazard ratio (HR) equal to 0.57, a total sample size of 94 patients is needed. As per standard practice in phase II trials, we used a one-sided alpha of 5% to test the superiority hypothesis, focusing on detecting a treatment benefit rather than testing for harm. This approach is justified by the exploratory nature of the trial, with the intent to generate efficacy signals to guide the design of a potential confirmatory phase III study. The sample size calculation is event-driven and based on detecting a hazard ratio (HR) of 0.57, assuming a 6-month PFS of 20% in the control arm and 40% in the experimental arm. A one-sided log-rank test with 5% type I error and 85% power was used. This corresponds to 91 required PFS events. The sample size of 94 patients (47 per arm) allows for adequate power, with an anticipated 10% dropout

rate bringing the planned enrollment to 104 participants. Sample size was computed using the "power logrank" command in Stata, applying the Schoenfeld formula.

PFS will be compared between regorafenib and the control arm when 91 PFS events are observed. The non-parametric Kaplan–Meier method will be used to estimate PFS and median survival time will be reported together with 95% confidence interval (CI) by Brookmeyer and Crowley. Comparisons between the two arms will be performed using the stratified log-rank test. A Cox proportional hazard model, with Efron's method of tie handling, including treatment and stratification factor at randomization as covariates will be used to assess the difference between the treatment arms. Superiority will be tested at 5% one-sided significant level.

The primary analysis will be performed in the ITT population, that is any subject included into the study, regardless of whether they received a study drug. No interim analyses for the primary endpoint are planned.

Data collection

Complete clinical and treatment information about patients enrolled in the study will be collected and recorded via an Electronic Data Capture System using the REDCap web application by study staff with confirmed Good Clinical Practice (GCP) certification named on delegation logs at the trial sites and will be stored in a secure database. Data collected during the course of the research will be kept strictly confidential and only accessed by members of the trial team. A sequential identification number will be automatically allocated to each patient registered in the trial. Data quality control and monitoring will be in charge of the Clinical Trial Unit. Missing data will not be imputed.

Reporting of adverse events indicating expectedness, seriousness, severity, and causality will be performed according to ICH GCP and EU Regulation 536/2014. At the trial sites, all reporting of adverse events must be done by the principal investigator or authorized staff member and will be transmitted electronically to Clinical Research Unit—IOV. As the sponsor, Istituto Oncologico Veneto IOV-IRCCS (Via Gattamelata 64, 35,128 Padua, Italy) will be responsible for the reporting of suspected unexpected serious adverse reaction (SUSARs)/unexpected serious adverse reaction (SARs) to the competent authorities, ethics committees, EudraVigilance Clinical Trial Module (EVCTM).

Study treatments

All participants will be randomly assigned to the intervention arm or control arm in a 1:1 ratio. Randomization will be performed using a computer-generated random assignment list. Patients will be randomized directly by the study promoter center on the IOV-IRCCS online randomization system (REDCap), accessible 24 h a day, 7 days a week, through the internet.

The randomization list will be made using block randomization and will be stratified by WHO grade (2 or 3). The study will be conducted in an open-label fashion.

Experimental arm: regorafenib

Patients randomized to the experimental arm will receive regorafenib 160 mg orally once daily for 3 weeks of every 4-week cycle. Each 160-mg dose will include four regorafenib 40-mg tablets. The selection of the study drug dose (160 mg daily) and dosing schedule (3 weeks on/1 week off) to be used in this study was based on available data from phase 2 study (REGOMA) [11]. Subjects will continue the assigned study treatment until disease recurrence, unacceptable toxicity, or death for any cause. Treatment will also be discontinued if the subject is unable to tolerate a daily dose of at least two tablets or a delay of more than 4 weeks from the due date for next administration of the drug is necessary. Dose adjustment guidelines are reported in Supplementary 1.

The main toxicities expected from the treatment are hand-foot skin reactions, hypertension and aspartate aminotransferase, alanine aminotransferase, and bilirubin elevation.

Control arm: local standard of care

Treatment in the control arm is left to the discretion of the investigator, according to local standard practice. Permitted drugs are, among the others, bevacizumab, hydroxyurea, and somatostatin analogs. Treatment will be continued until disease progression, unacceptable toxicity, or death for any cause. When applicable, recommendations for dose reduction will follow the guidelines contained within the relative summary of product characteristics (SmPC).

Study treatment accountability and compliance

For all study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk ware of the ingredients. The investigator is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Beginning from cycle 1, regorafenib accountability will be performed for each cycle. At the dispensing visit for each cycle, bottles must be returned

to the study site by participants with all unused medication. At the initial visit of each cycle, new regorafenib bottles will be dispensed. An adequate record of the receipt, distribution, and return of all study medication supplies will be recorded on the Study Drug Reconciliation and Destruction Log.

Subjects are required to record the self-administration of regorafenib daily dose (including the time of each intake) for the whole study duration in a paper diary that will be provided by the sponsor. Compliance to study drug will be evaluated every cycle by the investigational site and the reason(s) for any dose delay, reduction, or interruption have to be assessed and recorded. At each cycle, the completed diary will be collected and data recorded into the eCRF.

Concomitant medications

All concomitant drugs and combination therapies used from the beginning of the treatment protocol until 28 days after the final dose (when after-treatment is administered and up to the day before administration of after-treatment) will be recorded on a CRF. During the study, strong CYP3A4 inhibitors (e.g., clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole) or strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort) and strong UGT1A9 inhibitors (e.g., mefenamic acid, diflunisal, and niflumic acid) are not permitted.

SPIRIT reporting guidelines for publication of clinical trials protocols were used and were submitted as an additional file (see Additional file 1).

Study governance and trial sites

The MIRAGE trial is overseen by a study steering committee (SSC) composed of the principal investigator, co-investigators, and representatives from the Clinical Research Unit of IOV-IRCCS. The SSC is responsible for monitoring trial progress, protocol adherence, and participant safety. Regular meetings will be held to evaluate trial conduct and implement necessary modifications. The trial will be conducted across 15 specialized neuro-oncology centers in Italy, ensuring a broad patient recruitment base and high-quality data collection. The Istituto Oncologico Veneto IOV-IRCCS serves as the coordinating center, providing centralized oversight and data management. Each site will have dedicated clinical investigators trained in Good Clinical Practice (GCP) to ensure compliance with ethical and regulatory standards. Independent site monitoring will be conducted periodically to assess data integrity, protocol adherence, and patient safety. The trial will also undergo external auditing to verify compliance with regulatory requirements.

Discussion

Regorafenib showed antitumor activity in vitro and in vivo for meningiomas in a recent study; indeed, regorafenib demonstrated significant inhibition of meningioma cell motility and invasion and, in vivo, mice with orthotopic meningioma xenografts showed a reduced volume of signal enhancement in MRI following regorafenib therapy; this was translated in a significantly increased overall survival time ($p < 0.05$) for regorafenib-treated mice [12].

MIRAGE is the first prospective randomized phase II trial investigating the efficacy of regorafenib as first-line systemic therapy for patients with recurrent grade 2–3 meningiomas who are no longer eligible for loco-regional treatments. Patients will be enrolled in the MIRAGE trial according to the WHO 2021 classification. However, recent advancements in the molecular characterization of meningiomas, as outlined in the cIMPACT-NOW Update 8, suggest the potential need for a redefinition of diagnostic criteria. Specifically, cIMPACT8 introduced significant refinements in molecular markers, such as the loss of 1p combined with loss of 22q or NF2 oncogenic mutations which indicates a higher risk of recurrence and more aggressive behavior in meningioma grade 1 tumors [13]. These findings highlight the growing relevance of molecular parameters in refining diagnostic precision and therapeutic decision-making. They will be evaluated to be eventually incorporated in the additional molecular analyses within the MIRAGE trial. Such analyses could not only improve the interpretation of regorafenib efficacy but also contribute to the evolving integration of molecular diagnostics into clinical practice.

MIRAGE has been designed with an innovative and multidisciplinary approach, combining rigorous clinical research standards with advanced translational tools. The study has the potential to provide critical data on the management of recurrent meningiomas and to open new therapeutic perspectives. The outcomes of this study could represent a turning point in the management of these complex pathologies and significantly improve the quality of life for patients.

In conclusion, MIRAGE is the first prospective randomized clinical phase II trial comparing regorafenib with local standard of care and will provide robust data that might guide everyday practice in neuro-oncology.

Trial status

Protocol version 1.1 was approved on 5 June 2024. All amendments will be notified to the sites and to all competent authorities. 23 September 2024 is the date the

recruitment began. The approximate date when recruitment will be completed is Q1 2026.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-08997-2.

Additional file 1. SPIRIT checklist.

Additional file 2. Supplementary 1 Guidelines for regorafenib dose adjustment.

Acknowledgements
Not applicable.

Authors' contributions
GL is the principal investigator of the trial. AB and GC equally contributed to the first draft of the manuscript. PDB, MP, SM, SI, RM, GL, and GLD contributed to the study design and protocol development. All authors contributed to manuscript review, editing, and writing and read and approved the final manuscript.

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Data availability
All data generated in the study (e.g., eCRFs, the structured data files in the clinical database system, the results of the statistical evaluation and medical interpretation as well as the final clinical study report) are the property of the Istituto Oncologico Veneto. The sponsor (IOV-IRCCS) will have full access to the final trial dataset. Investigators from participating centers will also have access to the anonymized final dataset for scientific and publication purposes. No contractual agreements exist that restrict such access for investigators. Prior to submitting the results of this study for publication or presentation, the principal investigator will allow co-authors time to review and comment upon the publication manuscript.

Declarations

Ethics approval and consent to participate
All participating patients will provide written informed consent. Local investigators, who are board-certified physicians with up-to-date Good Clinical Practice (GCP) certification, confirmed delegation, and completed training for clinical trial activities, will be responsible for obtaining informed consent. Ethics approval for this study was obtained from the Ethics Committee of the Istituto Oncologico Veneto (Padua, Italy). The study was approved on June 5th, 2024, with protocol version 1.1. The trial is registered under EuCT number 2024–510954-28.

Consent for publication
This manuscript does not include any personally identifiable information from patients. No images or clinical details that could identify participants are presented in this report, nor will they be included in any future publications of the trial results. It is intended that the study design and main results will be published on www.clinicaltrials.gov. In addition, the results of the study may be published as scientific literature.

Competing interests
AB declares he has no competing interests. GC declares he has no competing interests. MP declares he has no competing interests. PDB declares he has no competing interests. MP declares he has no competing interests. SM declares he has no competing interests. SI declares he has no competing interests. RM declares he has no competing interests. GL declares he has no competing interests. MC declares he has no competing interests. MC declares he has no competing interests. MM declares he has no competing interests. SL has received honoraria for lectures, consultation, or advisory board participation from the following for-profit companies: Amgen, Merck Serono, Lilly, Servier, AstraZeneca, Incyte, Daiichi Sankyo, Bristol-Myers Squibb, MSD, Astellas Pharma, Bayer, GlaxoSmithKline, Takeda, Rottapharm Biotech, Beigene, Nimbus Therapeutics, Fosun Pharma, Roche, Pierre Fabre, GlaxoSmithKline. GDS declares he has no competing interests. GL has received honoraria for lectures, consultation, or advisory board participation from the following for-profit companies: Bayer, GlaxoSmithKline, Cecava, TME Pharma, Genenta Science, Novocure, Servier, Novartis, Janssen Oncology, Brain Health Solutions, health4u, Braun Travacare, CarThera.

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