BMC Cancer

STUDY PROTOCOL

Open Access

SENIPERA Phase 0/1 randomized window-of-opportunity clinical trial of SENIcapoc and PERAmpanel mono- and combination therapy of newly diagnosed glioblastoma: a trial protocol

Jens Toft Eschen[1,2], Line Louise Jensen[1,3], David Hausmann[4,5], Allice Nyborg Rosenkrans Lind[1,2], Slavka Lukacova[2,6], Joachim Weischenfeldt[7], Ulrik Lassen[8], Manfred Westphal[9], Frank Winkler[4,5], Ulf Simonsen[10] and Anders Rosendal Korshoej[1,2*]

Abstract

Background Glioblastoma is the most aggressive primary brain tumour in adults with a dismal prognosis and median overall survival of 12–14 months despite standard therapy. Novel discoveries in Cancer Neuroscience have revealed excitatory neuron-to-tumour synapses that drive glioma proliferation and invasion via AMPA-receptor activation, and vital tumour-autonomous calcium signalling mediated by KCa3.1 channels that sustain cancer cell network- and therapy resistance. Both mechanisms have been effectively targeted in preclinical studies using perampanel, a non-competitive AMPA-receptor antagonist, and senicapoc, a selective KCa3.1 blocker, suggesting promising avenues for treatment. This trial was designed to test the safety, pharmacokinetics, and biological effects of these drugs, as mono- and combination therapy, when added to standard-of-care treatment in newly diagnosed glioblastoma.

Methods SENIPERA is a two-stage, phase 0/1, prospective, open-label, randomised clinical trial with an exploratory window-of-opportunity design. A total of 27–36 adult patients with newly diagnosed glioblastoma will be enrolled. Trial Part A will enrol 9–18 patients in a 3 + 3 dose-escalation design to determine the maximum tolerable dose (MTD) of senicapoc. In Part B, 18 patients will be randomised 1:1 to receive perampanel monotherapy or combination therapy with senicapoc at the established MTD. Study treatment begins upon enrolment 7–14 days before surgery and continues until 30 days after adjuvant radiochemotherapy. Primary endpoints are the MTD of senicapoc (mg) (Part A) and the proportion of patients discontinuing perampanel due to intolerance at the lowest dose (Part B). Secondary endpoints include safety parameters, overall and progression-free survival, objective response rate, and

*Correspondence:
Anders Rosendal Korshoej
anders.r.korshoj@clin.au.dk

Full list of author information is available at the end of the article

tumour-volume changes. Exploratory analyses will characterise pharmacokinetics, tumour drug penetration, and molecular- genetic tumour profiles.

Discussion SENIPERA introduces a dual network-targeting strategy that simultaneously addresses neuronal-driven invasion and tumour network resilience in glioblastoma. By integrating senicapoc and perampanel with standard therapy in an early-phase, window-of-opportunity design, this study will establish the preliminary safety and pharmacological foundation for future trials evaluating safety and efficacy. The comprehensive translational analyses of tissue, cerebrospinal fluid, and blood will provide detailed insight into drug activity within the tumour microenvironment, informing the development of potential biologically guided treatment strategies for glioblastoma.

Trial registration EU-CT: 2025–522605-37–00.
Trial sponsor.
Aarhus University Hospital.
Department of Neurosurgery, Palle Juul-Jensens Boulevard 165, J617.
Aarhus, Denmark.
Protocol version and date.
Version 1.0
November 26, 2025.

Keywords Glioblastoma, Cancer neuroscience; window-of-opportunity trial, Phase 1, Senicapoc, Perampanel, Pacemaker cells

Introduction

Glioblastoma (GBM) is the most common primary brain cancer in adults. The disease is incurable and highly treatment resistant [1, 2]. The current standard of care includes maximal safe surgical resection, concomitant temozolomide (TMZ) and radiotherapy, and adjuvant maintenance chemotherapy. Despite these efforts, median survival remains 12–14 months from diagnosis, underscoring an urgent medical need for new and improved treatment options.

Recent advances in our understanding of the disease's interaction with the surrounding brain tissue and intricate mechanisms within the tumour that enable it to resist current treatment options, shed light on appealing new therapeutic targets [3]. At the tumour edge, GBMs consist of highly invasive and proliferating neural precursor- (NPC) and oligodendrocyte precursor (OPC) -like cells [4, 5], while the tumour core is dominated by mesenchymal (MES-like) cells interconnected by tumour microtubes [6, 7]. Excitatory glutamatergic synapses form between surrounding neurons and postsynaptic NPC/OPC-like cells, driving malignant invasion and growth through AMPA-receptor stimulation [8, 9].

Inhibition of the AMPA-receptor through pharmacological perturbation with perampanel has been shown to reduce proliferation of GBM cells and brain invasion in patient-derived xenograft (PDX) mouse models [8]. Perampanel, a non-competitive AMPA-receptor antagonist, is approved by the U.S. Food and Drug Administration and European Medicines Agency for add-on therapy in focal and generalized tonic–clonic epilepsy. It displays good blood–brain-barrier penetrance and advantageous pharmacokinetics, indicating promising clinical utility in GBM therapy.

Another recent study identified a novel subpopulation of pacemaker-like GBM cells with abundant potassium calcium channel 3.1 (KCa3.1) expression, which propagate vital intercellular Ca^{2+} waves through the tumour core, facilitating growth and resistance to chemo- and radiotherapy [10]. KCa3.1 generally regulates and maintains membrane potential and calcium influx, supporting pivotal cellular processes such as proliferation, migration, and cell cycle progression. Selective laser ablation of these pacemaker cells compromised GBM network communication and cancer cell survival, highlighting their vital role and potential as a new drug target. Correspondingly, pharmacological blockade of KCa3.1 with senicapoc, a drug deemed safe in phase IIb trials for sickle-cell anaemia and for COVID-19 [11, 12], reduced tumour growth and prolonged survival in animal models of GBM [10]. Furthermore, upregulation of the KCa3.1-encoding gene *KCNN4* has been linked to poor survival in patients with malignant gliomas and increased tumour invasion in vivo [13, 14]. These findings are consistent across several systemic cancers, including breast, pancreatic, and prostate [15–18]. Moreover, selective KCa3.1 blockers have been shown to enhance antitumor effects in systemic cancers and gliomas in vivo and in vitro, further supporting the role of KCa3.1 in malignant disease progression [19–21]. Notably, a study demonstrated improved survival of GL261-bearing mice when co-treated with the KCa3.1 antagonist TRAM-34 and

TMZ, compared with either TRAM-34 or TMZ alone. The study further demonstrated reduced cell viability and decreased proliferation rates of patient-derived cancer stem cells following co-treatment with TRAM-34 and TMZ using in vitro models [22].

Senicapoc furthermore displays good blood–brain barrier penetrance and an attractive tolerability profile. An ongoing phase IIa trial in the German Neuro-Oncological Working Group (NOA), the PerSurge trial, tests perampanel monotherapy in recurrent GBM [23]. In contrast, the combination with senicapoc and standard treatment has never been tested. As the biological mechanisms in question have been documented in xenograft models of newly diagnosed GBM (ndGBM) [8, 10], we aim to test the drugs in ndGBM patients, potentially with a higher benefit for patients with respect to tumour control, but potentially also associated with increased side effects. The compelling combination and patient tolerability of perampanel and senicapoc, targeting both the growth-stimulating neuron-to-tumour interactions and the intrinsic mechanisms that render GBM highly resistant to current standard-of-care, give rise to the SENIPERA-trial in ndGBM.

We hypothesise that simultaneous targeting of glioblastoma invasion and growth (via perampanel) and tumour resilience mechanisms (via senicapoc) represents a safe and biologically promising therapeutic strategy for ndGBM. The study aims to determine the safety and tolerability of each agent alone and in combination as add-on to standard therapy, characterise their pharmacokinetic profiles, and explore biological and clinical signals of therapeutic activity to inform subsequent phase 2 evaluation.

Methods

Trial design

The SENIPERA trial is a two-stage, phase 0/1, prospective, open-label, single-centre, randomised clinical study with an exploratory window-of-opportunity design. A total of 27–36 adult patients with suspected ndGBM will be enrolled. The study consists of two consecutive stages:

> Part A will include 9–18 patients and aims to determine the maximum tolerated dose (MTD) of senicapoc (Group 1).
> Part B will commence once the senicapoc MTD has been established. 18 patients will be randomised 1:1 to either receive perampanel monotherapy (Group 2) or the combination of perampanel with senicapoc at the MTD defined in Part A (Group 3).

In all arms, the investigational drugs will be administered in addition to standard-of-care therapy. A trial overview is depicted in Fig. 1.

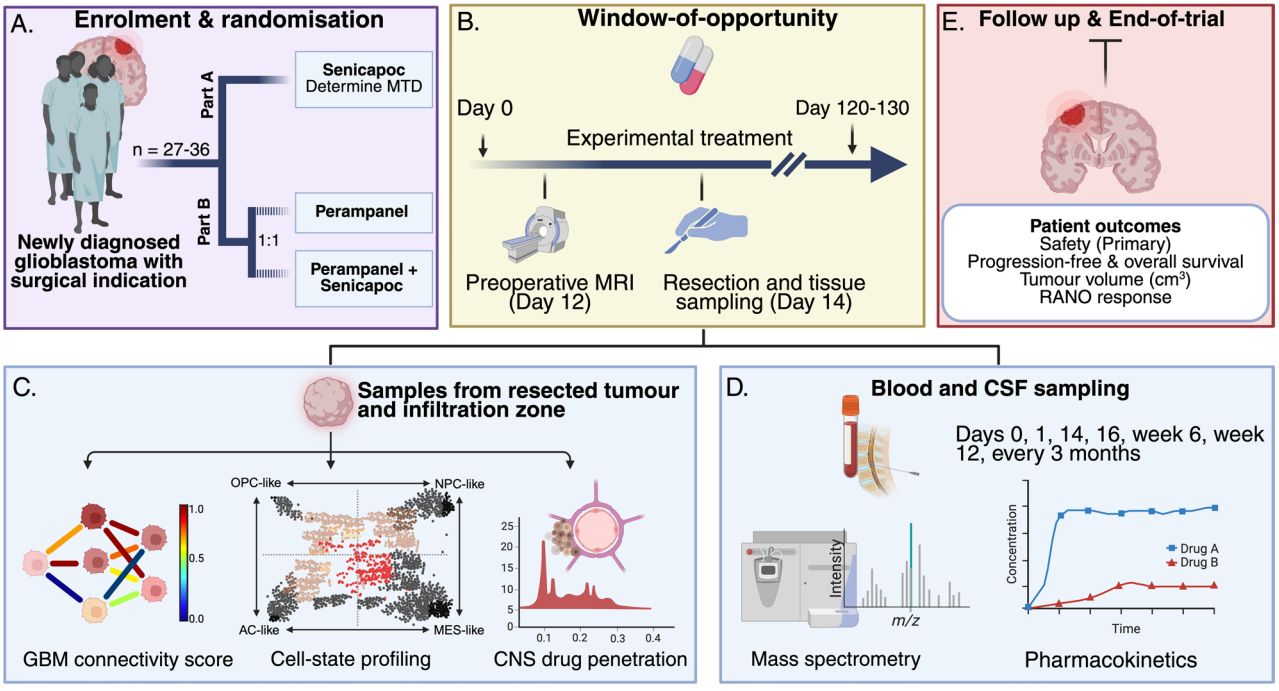

Fig. 1 Trial Overview. **A** Patient enrolment first into Part A of the trial to determine maximum tolerable dose (MTD) of senicapoc. After MTD has been determined, patients are randomised 1:1 to receive either perampanel or perampanel + senicapoc in trial Part B. **B**, **C** Experimental treatment two weeks prior to surgery enables detailed on-target pharmacokinetics and tumour-cellular profiling of the resected tumour tissue. **D** Systemic drug distribution is assessed through blood and cerebrospinal fluid samples obtained during surgery and scheduled hospital visits. **E** Safety profile, tumour volume and objective RANO response, and patient survival are assessed continuously until disease progression. Created with BioRender.com

Trial setting and duration

Patients will be enrolled and treated at the Department of Neurosurgery and Department of Oncology, Aarhus University Hospital, Denmark, between February 2026 and November 2028. Recruitment of 27–36 patients is anticipated to take approximately 24 months, while the exact number of included patients will depend on adverse events observed in the trial, in accordance with the modified 3 + 3 design of trial Part A. If a patient is excluded from the trial before the primary endpoint can be evaluated, an additional patient is enrolled. Part A is expected to be completed within 18 months (Q3/2027) and within 9 months for Part B (Q1/2028) (Fig. 2).

Eligibility criteria

Adult patients (minimum 18 years) with presumed GBM and planned neurosurgical tumour resection who fulfil all inclusion and no exclusion criteria will be eligible for trial enrolment. Eligibility criteria are identical in the trial's part A and part B.

Inclusion criteria

1. Presumed GBM as determined by an expert multidisciplinary neuro-oncological tumour board, including participants from neurosurgery, neuro-oncology, neurology, and neuroradiology. The assessment should be based on a whole-brain MRI according to the consensus recommendations for a standardised brain tumour imaging protocol in clinical trials, should be no older than 4 weeks from the assessment.
2. Eligibility for surgical resection and planned postoperative concomitant radiochemotherapy and adjuvant chemotherapy according to the Stupp regimen.

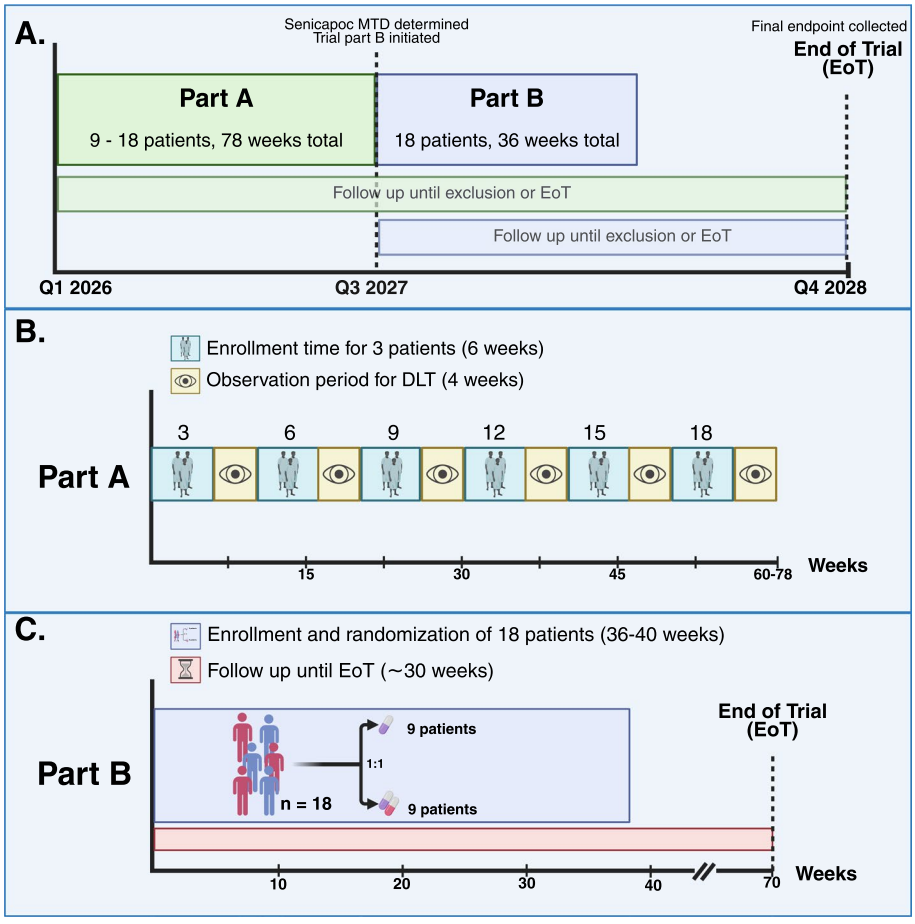

Fig. 2 Patient Recruitment Timeline. **A** Overview of expected timeline for participant enrolment in trial Part A and Part B. **B** Part A is expected to be completed within 18 months. It is dependent on the occurrence of dose-limiting toxicities in senicapoc monotherapy. Part A will establish the maximal tolerable dose of senicapoc for trial Part B. **C** 18 patients will be randomised 1:1 to receive standard therapy in combination with either perampanel or perampanel plus senicapoc, starting at the maximal tolerable dose established in Part A. All patients are followed until End of Trial. Created with BioRender.com

3. Eligible for safe postponement of surgery for 14 days from enrolment.
4. Life expectancy > 3 months.
5. WHO Performance Status ≤ 2.
6. Ability to sign written informed consent form
7. Use of validated anti-conception for fertile female participants in concordance with guidelines provided by the Danish health and medicines authority.

Exclusion criteria

1. Pregnancy or nursing. Fertile female participants will be required to take a validated pregnancy test for evaluation of pregnancy.
2. Previous treatment with or allergic reaction to perampanel or senicapoc.
3. Contraindications for senicapoc or perampanel treatment.
4. Previous malignancy with completion of treatment within five years before inclusion, except for basal cell carcinoma.
5. Concomitant intake of enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, phenobarbital, or primidone).
6. Significant co-morbidities, i.e.
    - Significant liver function impairment (ALAT > 210 µmol/L for men and > 135 µmol/L for women or total bilirubin > 25 µmol/L)
    - Significant impairment of renal function (eGFR < 60 mL/min/1.73 $m.^{2}$)
    - Coagulopathy (INR > 1.8 or aPTT > 57 s)
    - Thrombocytopenia (platelet count < 100 × $10.^{9}$/L)
    - Neutropenia (absolute neutrophil count < 1.5 × $10.^{9}$/L)
    - Anaemia (Hb < 6.0 mmol/L)
    - Severe cognitive impairment
7. Active participant in another therapeutic interventional clinical trial.
8. Any condition that might affect the absorption, distribution, metabolism, or excretion of the trial drugs (including malabsorption states).

Interventions

Study interventions will commence immediately upon enrolment to allow controlled drug exposure before surgery. Tumour resection and diagnostic biopsy will be performed within 14 days from inclusion, as mandated by Danish national cancer-care legislation, which further requires treatment to be initiated within 30 days of first patient contact. This window-of-opportunity design enables assessment of pharmacodynamic and pharmacokinetic effects directly in vivo in a pre-surgical setting.

Part A – senicapoc monotherapy

Dose escalation will follow a conventional 3 + 3 design to establish the maximum tolerated dose (MTD) of senicapoc monotherapy in Group 1, starting at the lowest dose level (DL 1) and proceeding stepwise according to observed dose-limiting toxicities (DLTs) (Fig. 3A). The MTD is defined as the highest dose level at which fewer than two of six patients experience a DLT during the first four weeks of treatment. Senicapoc will be administered orally twice daily from the day of inclusion (Days 1–2) and continued until 30 days after completion of radiochemotherapy (approximately day 120–130) (Fig. 4.).

Part B – perampanel monotherapy and perampanel and senicapoc combination therapy

After the establishment of the senicapoc MTD in Part A, Part B will randomise 18 patients (1:1) to receive either perampanel monotherapy (Group 2) or combination therapy with perampanel in combination with senicapoc (Group 3). For perampanel, dose escalation will begin at 2 mg once daily at bedtime and increase by 2 mg per week up to a maximum of 10 mg/day, depending on individual tolerability (Fig. 3B). The highest well-tolerated dose after four to six weeks will define the individual perampanel MTD.

In Group 3, patients will receive senicapoc at the MTD defined in Part A, together with perampanel titrated as described above. If intolerable toxicity occurs, the dose will be reduced to the previously well-tolerated level. Therapy may be discontinued if the lowest dose (2 mg perampanel or DL −2 senicapoc) is not tolerated.

For perampanel, if side effects such as dizziness, drowsiness, fatigue, nausea, confusion, irritability, gait instability, coordination, or mental changes occur after dose escalation, the dose will be reduced to the previously well-tolerated level. Senicapoc is generally well tolerated [24]; the most commonly observed events are mild gastrointestinal symptoms (e.g., diarrhea, nausea, constipation). No severe adverse events or anaphylactic reactions have been reported for senicapoc in the reviewed clinical trial data [11].

All patients will be monitored for an additional 30 days for treatment-related delayed toxicities. DLTs for both drugs are defined as adverse events graded ≥ 3 according to CTCAE version 5.0 or toxicities leading to treatment discontinuation that are definitely, probably, or possibly related to the investigational product. The investigators will perform dose adjustments and DLT management according to individual clinical assessment.

Standard therapy

All participants will receive standard-of-care neurosurgical and neuro-oncological treatment in accordance with the Danish Neuro-Oncology Group glioma guidelines

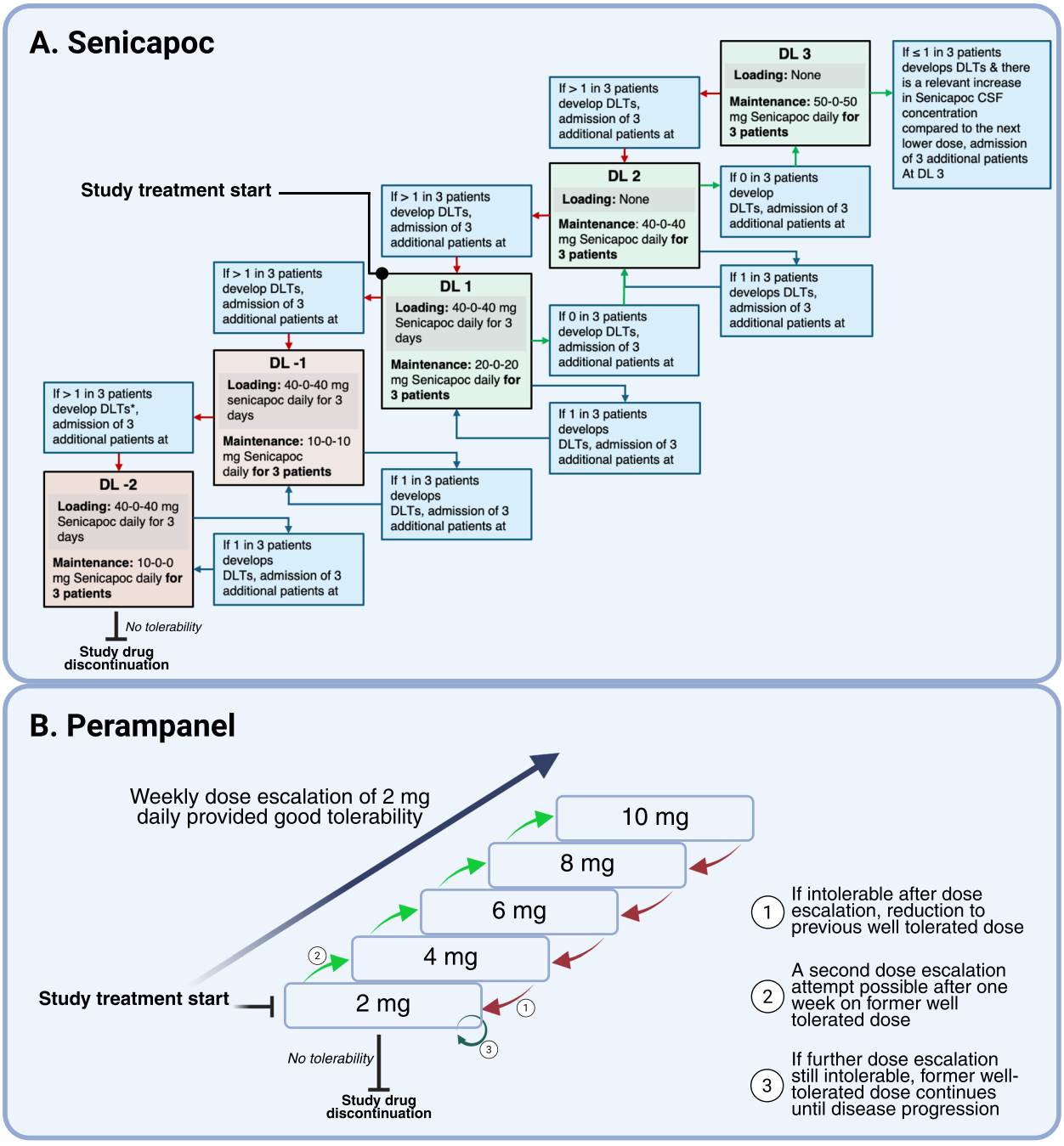

Fig. 3 Dose Escalation Regimens. Panel **A** Dose-limiting toxicities are defined as all AEs coded using MedDRA ≥ Grade 3 according to the CTCAE v5.0 or intolerable toxicities that lead to the withdrawal of the patient from the trial that are definitely, probably, or possibly related to the administration of the investigational agents in combination with the SOC therapy or perampanel. DLTs only in the first 30 days from the start of therapy are used to guide dose de- or escalation. If ≤ 1 of 6 patients in a dose-cohort have developed DLT, this is the maximum tolerable dose (MTD). Limitation: The MTD is being used for the phase II part of this trial unless no relevant increase in cerebrospinal fluid concentration (defined as increase in average concentration by ≥ 10%) of senicapoc is achieved by the MTD in comparison to the next lower dose-cohort. In this case, the next lower dose is used to avoid an unnecessary burden of toxicities. Panel **B** Patients follow standard individual tolerance-dependent perampanel dose escalation of 2 mg per week up to a maximal 10 mg daily. Created with BioRender.com

[25]. Patients will undergo fluorescein- or 5-ALA-guided maximal safe resection performed by trained neurosurgeons. After surgery, all participants will receive concomitant radiochemotherapy following the Stupp regimen [26]: intensity-modulated radiotherapy (60 Gy in 30 fractions over 6 weeks) with daily temozolomide (75 mg/m^2), followed by adjuvant temozolomide (150–200 mg/m^2 for 5 days every 28 days, for six cycles). Supportive

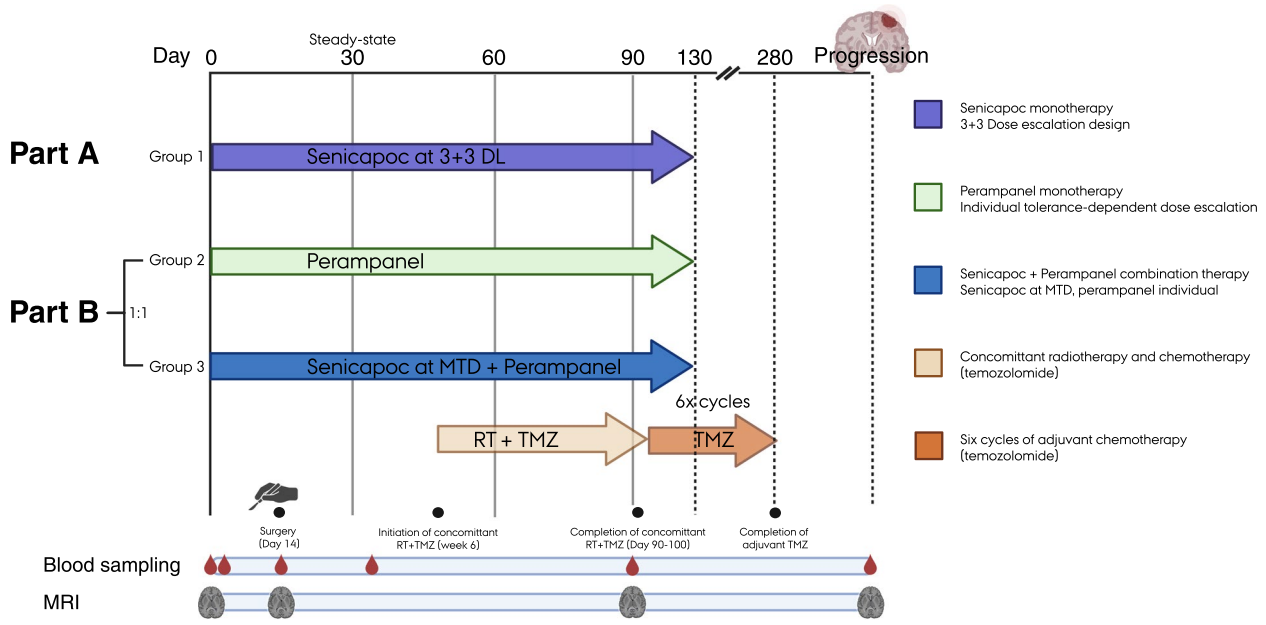

Fig. 4 Overview of trial drug exposure times and interventions. Created with BioRender.com

or palliative medication, including corticosteroids, is permitted as clinically indicated. Eligible patients may undergo repeated surgical resection upon disease progression. For such cases, tissue, blood, plasma, and cerebrospinal fluid (CSF) samples may be collected as described for the primary surgery to evaluate the biological effects of long-term exposure to perampanel and/or senicapoc.

Outcomes

Primary endpoints

In Part A, the primary endpoint is the MTD of senicapoc during the first four weeks of treatment. In Part B, the primary endpoint is the proportion of patients in Groups 2 and 3 who discontinue perampanel due to intolerability at the lowest daily dose (2 mg) within the first six weeks of treatment.

Secondary endpoints

The safety of the trial intervention will be assessed by the incidence, type, and severity of adverse events (AEs) and serious adverse events (SAEs) in each treatment group, graded according to Common Terminology Criteria for Adverse Events (CTCAE version 5.0). All AEs will be summarised by frequency, grade, and relationship to study medication from inclusion until 30 days after treatment completion.

Overall survival (OS; time from randomisation to death from any cause) and progression-free survival (PFS; time from randomisation to disease progression per RANO 2.0 criteria or death) [27] will be evaluated as secondary outcomes. Objective response rate (ORR; proportion of patients achieving a complete or partial response per RANO 2.0 criteria) will also be assessed. Tumour volumes will be quantified from T2/FLAIR and contrast-enhanced T1 MRI sequences, and absolute and relative changes will be evaluated longitudinally from baseline to follow-up MRIs.

Exploratory translational endpoints

Exploratory analyses will characterise pharmacokinetic, molecular, and biomarker responses to treatment. Serum concentrations of senicapoc and perampanel will be measured to estimate pharmacokinetic parameters and evaluate brain and CSF penetration by comparing drug levels in plasma, CSF, and tumour tissue. Molecular profiling of resected tumour tissue will assess treatment-related cellular and transcriptional changes, including subtype composition, differential gene expression, and pathway activation. Associations between molecular or epigenetic biomarkers and clinical outcomes will be explored, including O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, CHI3L1-based connectivity scores [28], and neural epigenetic signatures [29].

Harms

AEs are defined as any untoward medical occurrence in a participant receiving study medication, whether considered related to the investigational product or not. AEs will be documented and graded according to CTCAE version 5.0 [30]. This includes new symptoms, worsening of baseline neurological or physical findings, and clinically relevant abnormalities in vital signs, electrocardiography, or laboratory parameters. Each event will be evaluated by

the investigator for seriousness, severity, expectedness, and relationship to the study treatment. SAEs are defined as events resulting in death, being life-threatening, requiring or prolonging hospitalisation, causing persistent or significant disability, or otherwise deemed medically important. SAEs will be reported to the sponsor within 24 h of site awareness and reviewed in accordance with Danish and European legislation. The investigator will assess the causality of each AE and the sponsor will review it, considering the temporal relationship to study drug administration, biological plausibility, and alternative explanations. Both investigator and sponsor assessments will be documented, and in cases of disagreement the more conservative judgement will be used for regulatory reporting. The expectedness of adverse reactions will be determined against the Reference Safety Information (RSI) in the Investigator's Brochures, and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported to the competent authorities. All AEs will be followed until resolution or stabilisation and summarised by frequency, grade, and attribution in the final analysis.

Participant timeline and schedule of assessments

Participants will be followed regularly throughout the interventional treatment and observation periods, in accordance with local clinical guidelines. Scheduled clinical evaluations, laboratory tests, and MRI assessments are summarised in Fig. 4, illustrating the timing of enrolment, investigational treatment, surgery, and follow-up procedures at the participant level. Exact details on timing is provided in Supplementary Table 1. The frequency or scope of follow-up may be adjusted at the discretion of the treating physician if clinically indicated, for example in cases of suspected disease progression or treatment-related toxicity. The total duration of study participation is expected to be less than 12 months for most patients, based on the median PFS in ndGBM [31].

Sample size

This early-phase, exploratory study will enrol 27–36 patients across three treatment groups. The sample size is based on feasibility and established principles for Phase 0/1 studies, ensuring adequate assessment of DLTs, pharmacokinetics, and preliminary efficacy. In Group 1 (trial part A), dose escalation will follow a modified 3 + 3 design to determine the MTD of senicapoc, defined as the highest dose level at which fewer than two of six patients experience a DLT. In Groups 2 and 3 (trial part B), tolerability of perampanel monotherapy and the senicapoc–perampanel combination will be considered acceptable if fewer than three of nine patients discontinue treatment due to drug-related toxicity during the initial 6-week exposure period at the lowest perampanel dose (2 mg).

Randomisation and blinding

A senior statistician will generate the allocation sequence to assign patients to the two treatment groups (2 and 3) without stratification. Randomization in Part B will be performed using the randomization module in the Research Electronic Data Capture (REDCap) platform. The randomization sequence will be provided to the REDCap administrator. All study data will be entered in the secure REDCap database with audit trails and role-based access. No study personnel will have access to the allocation sequence, and as this is an open-label study**,** neither participants, investigators, nor outcome assessors will be blinded to treatment allocation.

Data collection and management

Tissue sampling and biological materials

The planned sampling of tumour tissue, blood, and CSF after drug exposure allows for characterisation of drug penetration and pharmacokinetics, and identification of early biological responses to treatment. While the principal objective is to establish the safety and tolerability of senicapoc alone and in combination with perampanel, inclusion of a perampanel monotherapy arm also permits comparative analyses of clinical, radiological, and molecular endpoints to explore potential additive or synergistic effects. Efficacy endpoints will serve as early indicators of therapeutic activity, informing the selection of treatment arms for subsequent phase 2 evaluation and enabling refinement of sample-size calculations for studies with definitive clinical efficacy endpoints. A schematic overview of the trial structure, timelines, and assessments is provided in Fig. 1.

Blood

Peripheral blood will be collected seven times during the study, primarily in connection with routine clinical visits. Baseline haematology and clinical chemistry will be assessed at enrolment (Day 0) and again during the loading phase (Days 1–3) for pharmacokinetic evaluation of trial drugs. Additional blood samples will be obtained at the time of surgery (approximately Day 12–14), post-operatively (Days 14–16), at Week 6 (initiation of concomitant radiochemotherapy), at Week 12 (completion of radiochemotherapy), and subsequently every three months during adjuvant temozolomide therapy in conjunction with scheduled follow-up MRI visits. Blood samples will be used for pharmacokinetic analyses**,** including measurement of serum concentrations of senicapoc and perampanel**,** and for translational studies investigating treatment-induced systemic changes. These analyses will both establish the germline genetic background (serving as a reference for distinguishing inherited from tumour-specific mutations) and assess tumour-derived alterations, including circulating tumour

cells (CTCs), fractions of cell-free DNA/RNA (cfDNA, cfRNA), and tumour-derived DNA/RNA (ctDNA, ctRNA). Additional analyses will include peripheral blood mononuclear cells (PBMCs), extracellular vesicles (EVs), and protein biomarkers.

Cerebrospinal fluid

Longitudinal CSF samples will be collected for pharmacokinetic and translational analyses. The first sample will be obtained intraoperatively (Days 12–14), either by lumbar puncture or via perioperative access to the subarachnoid space. During surgery, all patients will have an Ommaya reservoir placed in a subgaleal pocket over the resection cavity to enable repeated, minimally invasive CSF sampling. Subsequent samples will be collected post-operatively (Days 14–16), at Weeks 6 and 12, and every three months during adjuvant temozolomide therapy, aligned with blood sampling and follow-up visits.

Tumour tissue

During neurosurgical resection, tumour tissue will be collected for diagnostic purposes and for pharmacokinetic and translational analyses. Each sample will be obtained under neuronavigation guidance and annotated, with specimens taken from both the tumour core and the peritumoural infiltration zone when deemed safe by the responsible neurosurgeon. The resected material will be used to determine intratumoural concentrations of the investigational drugs and to characterise treatment-induced molecular changes using single-cell RNA sequencing to assess cellular heterogeneity, transcriptional responses, and potential resistance mechanisms. Additional analyses will include mass-spectrometry-based protein profiling and digital spatial profiling to map protein and gene expression within the tumour microenvironment.

Strategies to improve study adherence

To enhance participant adherence to the intervention protocols, the following strategies will be implemented: Oral dosing will be simplified with clear, easy-to-follow instructions, and pre-packed pill organizers will be provided to facilitate medication management. Comprehensive education about the trial, the medications, and the importance of adherence will be provided to participants and their caregivers at the start of the trial and upon request. Regular follow-up and communication will be maintained throughout the trial, and a dedicated contact person from the study team will be available to resolve any possible inquiries or issues.

Data monitoring committee and oversight

Safety data will be continuously reviewed by the investigators and the Data Safety Monitoring Committee (DSMC), which oversees participant safety and trial conduct throughout the study. The DSMC will consist of specialists in neuro-oncology, neurosurgery, and biostatistics, as well as a patient representative, all independent of the sponsor and investigators. Its primary responsibilities are to monitor accumulating safety data, including DLTs and SAEs, and to advise on trial continuation, modification, or termination.

Only DSMC members will have access to interim safety data. The committee will meet after completion of each dose cohort in Part A, after enrolment of 50% of participants in Part B, and as needed in response to safety concerns. Following each review, the DSMC will issue written recommendations to the Principal Investigator and the independent Trial Steering Committee (TSC). Overall trial governance is provided by the TSC, composed of international clinical and scientific experts in neuro-oncology and neurosurgery, including representatives from Rigshospitalet (Denmark), Heidelberg University Hospital (Germany), and the University Medical Center Hamburg–Eppendorf (Germany), as well as the principal and co-investigators at Aarhus University Hospital. The TSC oversees scientific integrity, ethical standards, and strategic trial conduct, and serves as the final decision-making body for protocol modifications or trial termination following DSMC recommendations.

Trial monitoring and termination

Monitoring of compliance with International Council for Harmonisation Good Clinical Practice (ICH-GCP) will be performed by the GCP Unit at Aarhus University. End-of-trial is defined as one year after the last patient in Part B completes treatment. The study may, however, be suspended or terminated earlier under the following circumstances. If more than one-third of participants in any treatment group experience drug-related serious adverse reactions (SARs), that group will be closed. If more than one-third of all enrolled participants across groups experience drug-related SARs, the trial will be temporarily suspended for safety review by the DSMC. The trial may also be terminated if recruitment rates fall substantially below projections, making it unlikely to achieve the planned sample size within a reasonable timeframe. Finally, termination may be considered if changes in the standard of care render the design obsolete or unethical, or if new safety information materially alters the risk–benefit profile of the study drugs.

Statistical methods

Safety endpoints will be summarised descriptively. AE frequencies will be compared between groups using Fisher's exact test. OS and PFS will be analysed using Kaplan–Meier methods, with log-rank comparisons. ORR will be reported with exact 95% confidence intervals

for each group. Longitudinal tumour-volume changes will be assessed using mixed-effects models to account for repeated measurements over time.

Given the exploratory nature of this phase 0/1 trial, all statistical tests will be two-sided with a significance level of 0.10, and no adjustment for multiple-testing will be performed. Results will be interpreted cautiously considering the multiple comparisons performed. Analyses will follow the intention-to-treat principle, with per-protocol analyses for sensitivity excluding patients with major protocol violations. Missing data will be handled according to standard statistical practice. For time-to-event outcomes, patients lost to follow-up will be censored at the last known contact. For longitudinal endpoints, mixed-effects models will be applied, which are robust to missing data under the missing-at-random assumption. Multiple imputation will be used for other outcomes with missing values, and sensitivity analyses will assess the impact of missing data on study conclusions. No formal interim analyses for efficacy are planned due to the small sample size; however, continuous safety monitoring will be performed by the independent DSMC.

Patient and public involvement

Patients and the public were not involved in the design, conduct, or reporting of this trial.

Discussion

Glioblastoma remains one of the most treatment-resistant human malignancies, with current multimodal therapy providing only a modest survival benefit. The SENIPERA trial addresses this urgent clinical need by translating novel insights into glioblastoma biology—specifically the roles of excitatory neuron-to-tumour signalling and tumour-cell network resilience—into a mechanism-driven early-phase clinical trial. By selectively inhibiting AMPA-receptors with perampanel and blocking KCa3.1 with senicapoc, the trial aims to disrupt complementary mechanisms that drive invasion and treatment resistance in ndGBM.

The PerSurge trial investigates perampanel monotherapy in recurrent GBM [23], while SENIPERA applies a similar network-targeting approach to newly diagnosed disease—the stage that most closely mirrors the patient-derived xenograft models in which the underlying biology was discovered [8, 10]. This window-of-opportunity design allows direct evaluation of drug exposure, pharmacokinetics, and molecular effects in vivo without delaying standard therapy. The incorporation of paired tumour, cerebrospinal fluid, and blood sampling will generate a multidimensional dataset linking pharmacological parameters with cellular and transcriptional responses. These analyses may clarify how AMPA-receptor and KCa3.1 signalling influence tumour heterogeneity, treatment response, and resistance mechanisms in the primary tumour.

Beyond its translational value, SENIPERA is designed to define safety and tolerability parameters essential for advancing both drugs into later-phase clinical testing. Because senicapoc and perampanel are repurposed agents with established safety in non-oncological indications, the trial combines scientific innovation with a favourable risk–benefit profile. Its two-stage structure, incorporating dose escalation and randomisation, ensures rigorous and safe assessment of toxicity, pharmacokinetics, and early efficacy signals within a controlled, ethically sound framework.

Furthermore, future studies may consider stratifying participants by MGMT-promoter methylation status or focusing on MGMT-unmethylated GBM, given that TMZ offers limited benefit in these patients and the need for alternative therapeutic strategies is particularly pressing [1].

If successful, SENIPERA will establish the foundation for a future phase 2 trial exploring combined network-targeting therapy in glioblastoma. The study may also yield new biomarkers for treatment response and patient stratification, guiding more individualised therapeutic strategies. By bridging mechanistic neuroscience and clinical neuro-oncology, the SENIPERA trial represents an important step toward biologically informed, multimodal therapy for this devastating disease.

Abbreviations

AE	Adverse event
CNS	Central nervous system
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DL	Dose level
DLT	Dose limiting toxicity
DSMC	Data Safety Monitoring Committee
GBM	Glioblastoma
KCa3.1	Potassium-activated calcium channel 3.1
MES	Mesenchymal-like
MTD	Maximum tolerable dose
ndGBM	Newly diagnosed glioblastoma
NPC	Neural precursor-like
OPC	Oligodendrocyte precursor-like
OR	Overall survival
ORR	Objective response rate
PDX	Patient-derived xenograft
PFS	Progression-free survival
RANO	Response assessment in neuro-oncology
SAE	Serious adverse event
TMZ	Temozolomide
TSC	Trial steering committee

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-026-15784-y.

Supplementary Material 1.

Supplementary Material 2.

Acknowledgements
We thank the Department of Neurosurgery and Oncology at Aarhus University Hospital for their enthusiastic support for this study. We further thank Herlev Pharma Service ApS for their assistance with the importation, GMP handling, packaging, and labelling of senicapoc tablets used in this trial. The authors used generative artificial intelligence (OpenAI, ChatGPT-5.1) to assist with language editing of this manuscript. Authors are fully responsible for the content.

Dissemination policy
Trial results, including AEs and SAEs, will be published in peer-reviewed international journals and presented at relevant scientific conferences. A summary of trial results will be submitted to the EU Clinical Trials Information System (CTIS) within one year of completion, in accordance with EU Regulation No. 536/2014. Authorship will follow the International Committee of Medical Journal Editors (ICMJE) and CRediT guidelines. The full study protocol and statistical analysis plan will be made publicly available through open-access repositories.

Authors' contributions
Drafting of the manuscript: JTE, ARK; All Authors read, edited, and approved the final manuscript.

Funding
This study is fully funded by the Independent Research Fund Denmark (grant no. 4308-00118B9 and the Novo Nordisk Foundation (grant no. NNF24OC0095318). All funders have no role in study design, conduct, analysis, or the decision to publish.

Data availability
Data sharing is not applicable to this article as no datasets were yet generated or analysed during the current study. Anonymised participant-level data and other relevant study documents will be made available in accordance with FAIR principles (e.g. Zenodo.org) through open-access repositories after publication of primary results. Access to de-identified data may be granted upon reasonable request to the sponsor, in compliance with applicable European data protection legislation (GDPR) and Danish law.

Declarations

Ethics approval and consent to participate
The study has been approved by the Danish Medicines Agency (*Lægemiddelstyrelsen*) and by the National Committee on Health Research Ethics (*De Videnskabsetiske Medicinske Komitéer*) (EU-CT: 2025–522605-37–00, authorized 14 October 2025). The trial will be conducted in accordance with the principles of the Declaration of Helsinki, the ICH-GCP guidelines, and all applicable Danish and European legislation. Written informed consent will be obtained from all participants before any trial-related activities by a qualified study team member. It may be withdrawn at any time without consequences for subsequent clinical care in accordance with Danish legislation. The Danish Patient Compensation Association will cover all patient injuries.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Neurosurgery, Aarhus University Hospital, Aarhus, Denmark
[2]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
[3]Department of Neurology, Physiotherapy, and Occupational Therapy, Gødstrup Regional Hospital, Herning, Denmark
[4]Department of Neurology, University Hospital Heidelberg, and National Center for Tumor Diseases, Heidelberg, Germany
[5]Clinical Cooperation Unit Neurooncology, German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany
[6]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark
[7]Biotech Research & Innovation Center (BRIC), University of Copenhagen and Finsen Laboratoriet, Copenhagen University Hospital, Copenhagen, Denmark
[8]Department of Oncology, Copenhagen University Hospital, Copenhagen, Denmark
[9]Institute for Tumor Biology, Universitätskrankenhaus Hamburg Eppendorf, Hamburg, Germany
[10]Department of Biomedicine, Aarhus University, Aarhus, Denmark

Received: 25 November 2025 / Accepted: 19 February 2026
Published online: 14 April 2026

References

1. Weller M, Wick W, Aldape K, Brada M, Berger M, Pfister SM, et al. Glioma. Nat Rev Dis Primers. 2015;1(1):15017–15017.
2. Ostrom QT, Price M, Neff C, Cioffi G, Waite KA, Kruchko C, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2015–2019. Neuro-oncology (Charlottesville, Va). 2022;24(Supplement_5):v1–95.
3. Pan C, Winkler F. Insights and opportunities at the crossroads of cancer and neuroscience. Nat Cell Biol. 2022;24(10):1454–60.
4. Greenwald AC, Darnell NG, Hoefflin R, Simkin D, Mount CW, Gonzalez Castro LN, et al. Integrative spatial analysis reveals a multi-layered organization of glioblastoma. Cell. 2024;187(10):2485-2501.e26.
5. Winkler F, Venkatesh HS, Amit M, Batchelor T, Demir IE, Deneen B, et al. Cancer neuroscience: state of the field, emerging directions. Cell. 2023;186(8):1689–707.
6. Weil S, Osswald M, Solecki G, Grosch J, Jung E, Lemke D, et al. Tumor microtubes convey resistance to surgical lesions and chemotherapy in gliomas. Neuro-oncol. 2017;19(10):1316–26.
7. Osswald M, Jung E, Sahm F, Solecki G, Venkataramani V, Blaes J, et al. Brain tumour cells interconnect to a functional and resistant network. Nature (London). 2015;528(7580):93–8.
8. Venkataramani V, Tanev DI, Strahle C, Studier-Fischer A, Fankhauser L, Kessler T, et al. Glutamatergic synaptic input to glioma cells drives brain tumour progression. Nature (London). 2019;573(7775):532–8.
9. Venkataramani V, Yang Y, Schubert MC, Reyhan E, Tetzlaff SK, Wißmann N, et al. Glioblastoma hijacks neuronal mechanisms for brain invasion. Cell. 2022;185(16):2899-2917.e31.
10. Hausmann D, Hoffmann DC, Venkataramani V, Jung E, Horschitz S, Tetzlaff SK, et al. Autonomous rhythmic activity in glioma networks drives brain tumour growth. Nature. 2023;613(7942):179–86.
11. Ataga KI, Smith WR, De Castro LM, Swerdlow P, Saunthararajah Y, Castro O, et al. Efficacy and safety of the Gardos channel blocker, senicapoc (ICA-17043), in patients with sickle cell anemia. Blood. 2008;111(8):3991–7.
12. Granfeldt A, Andersen LW, Vallentin MF, Hilberg O, Hasselstrøm JB, Sørensen LK, et al. Senicapoc treatment in COVID-19 patients with severe respiratory insufficiency—A randomized, open-label, phase II trial. Acta Anaesthesiologica Scandinavica. 2022;66(7):838-46. https://doi.org/10.1111/aas.14072.
13. Turner KL, Honasoge A, Robert SM, McFerrin MM, Sontheimer H. A proinvasive role for the Ca2+-activated K+ channel KCa3.1 in malignant glioma. Glia. 2014;62(6):971–81.
14. Lehrer S, Rheinstein PH. Increased KCNN4 expression is correlated with poor survival in lower grade glioma. Cancer Diagn Progn. 2023;3(4):428–32.
15. Lallet-Daher H, Roudbaraki M, Bavencoffe A, Mariot P, Gackière F, Bidaux G, et al. Intermediate-conductance Ca2+-activated K+ channels (IKCa1) regulate human prostate cancer cell proliferation through a close control of calcium entry. Oncogene. 2009;28(15):1792–806.
16. Mohr CJ, Gross D, Sezgin EC, Steudel FA, Ruth P, Huber SM, et al. KCa3.1 channels confer radioresistance to breast cancer cells. Cancers (Basel). 2019;11(9):1285.
17. Bonito B, Sauter DRP, Schwab A, Djamgoz MBA, Novak I. KCa3.1 (IK) modulates pancreatic cancer cell migration, invasion and proliferation: anomalous effects on TRAM-34. Pflugers Arch. 2016;468(11–12):1865–75.
18. Mohr CJ, Steudel FA, Gross D, Ruth P, Lo WY, Hoppe R, et al. Cancer-associated intermediate conductance Ca2+-activated K+ channel KCa3.1. Cancers (Basel). 2019;11(1):109.
19. Bachmann M, Rossa A, Varanita T, Fioretti B, Biasutto L, Milenkovic S, et al. Pharmacological targeting of the mitochondrial calcium-dependent

potassium channel KCa3.1 triggers cell death and reduces tumor growth and metastasis in vivo. Cell Death Dis. 2022;13(12):1055–19.
20. Bauer D, Werth F, Nguyen HA, Kiecker F, Eberle J. Critical role of reactive oxygen species (ROS) for synergistic enhancement of apoptosis by vemurafenib and the potassium channel inhibitor TRAM-34 in melanoma cells. Cell Death Dis. 2017;8(2):e2594–e2594.
21. Grimaldi A, D'Alessandro G, Golia MT, Grössinger EM, Di Angelantonio S, Ragozzino D, et al. KCa3.1 inhibition switches the phenotype of glioma-infiltrating microglia/macrophages. Cell Death Dis. 2016;7(4):e2174–e2174.
22. D'Alessandro G, Grimaldi A, Chece G, Porzia A, Esposito V, Santoro A, et al. KCa3.1 channel inhibition sensitizes malignant gliomas to temozolomide treatment. Oncotarget. 2016;7(21):30781–96.
23. Heuer S, Burghaus I, Gose M, et al. PerSurge (NOA-30) phase II trial of perampanel treatment around surgery in patients with progressive glioblastoma. BMC Cancer. 2024;24:135. https://doi.org/10.1186/s12885-024-11846-1.
24. Ataga KI, Orringer EP, Styles L, Vichinsky EP, Swerdlow P, Davis GA, et al. Dose-escalation study of ICA-17043 in patients with sickle cell disease. Pharmacotherapy. 2006;26(11):1557–64.
25. Dansk Neuro-Onkologisk Gruppe. Gliomer hos voksne | Kliniske retningslinjer . 2024. Available from: https://dnog.dk/onewebmedia/files/Retningslinier%20PDF/DNOG_Gliomer_v4.0_AdmGodk_161224.pdf. Cited 22 Mar 2025.
26. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987–96.
27. Wen PY, van den Bent M, Youssef G, Cloughesy TF, Ellingson BM, Weller M, et al. RANO 2.0: Update to the Response Assessment in Neuro-Oncology Criteria for High- and Low-Grade Gliomas in Adults. Journal of clinical oncology. 2023;41(33):5189–99.
28. Hai L, Hoffmann DC, Wagener RJ, Azorin DD, Hausmann D, Xie R, et al. A clinically applicable connectivity signature for glioblastoma includes the tumor network driver CHI3L1. Nature Communications. 2024;15(1):968. https://doi.org/10.1038/s41467-024-45067-810.1038/s41467-024-45067-8.
29. Drexler R, Khatri R, Sauvigny T, Mohme M, Maire CL, Ryba A, et al. A prognostic neural epigenetic signature in high-grade glioma. Nat Med . 2024 May 17; Available from: https://www.nature.com/articles/s41591-024-02969-w.
30. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. 2017. Available from: https://www.meddra.org/.
31. Ballman KV, Buckner JC, Brown PD, Giannini C, Flynn PJ, LaPlant BR, et al. The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme. Neuro Oncol. 2007;9(1):29–38.

Publisher's note