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Low & Anaplastic Grade Glioma Umbrella Study of MOlecular Guided TherapieS (LUMOS-2): study protocol for a phase 2, prospective, multicentre, open-label, multiarm, biomarker-directed, signal-seeking, umbrella, clinical trial for recurrent IDH mutant, grade 2/3 glioma

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ABSTRACT

Introduction All grade 2/3 gliomas are incurable and at the time of inevitable relapse, patients have significant unmet needs with few effective treatments. This study aims to improve outcomes by molecular profiling of patients at relapse, then matching them with the best available drug based on their molecular profile, maximising the chances of patient benefit while simultaneously testing multiple novel drugs.

Methods and analysis Low & Anaplastic Grade Glioma Umbrella Study of MOlecular Guided TherapieS (LUMOS-2) will be an international, phase 2, multicentre, open-label, biomarker-directed, umbrella clinical trial for recurrent isocitrate dehydrogenase mutant, histologically grade 2/3 gliomas. Investigational treatment will be assigned based on molecular profiling of contemporaneous tissue obtained at disease relapse using next-generation sequencing. LUMOS-2 will begin with three therapeutic treatment arms: paxalisib, cadonilimab and selinexor. Patient molecular profiles will be assessed by an expert, multidisciplinary Molecular Tumour Advisory Panel. Patients whose molecular profile is considered suitable for a targeted agent like paxalisib will be allocated to that arm, others will be randomised to the available arms of the trial. The primary endpoint is progression-free survival at 6 months. Secondary objectives include assessment of overall survival, response rate, safety and quality of life measures. Two additional therapeutic arms are currently in development.

Ethics and dissemination Central ethics approval was obtained from the Sydney Local Health District Ethics Review Committee, Royal Prince Alfred Hospital Zone, Sydney, Australia (Approval: 2022/ETH02230). Other clinical sites will provide oversight through local governance processes, including obtaining informed consent from suitable participants. A report describing the results of the study will be submitted to international meetings and peer-reviewed journals.

Trial registration number ACTRN12623000096651.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Low & Anaplastic Grade Glioma Umbrella Study of MOlecular Guided TherapieS (LUMOS-2) will be an umbrella clinical trial for recurrent isocitrate dehydrogenase mutant, histologically grade 2/3 glioma evaluating targeted or novel therapies for signals of clinical efficacy.

⇒ This study will perform next-generation sequencing on relapsed tumour tissue to inform the selection of targeted treatments by a Molecular Tumour Advisory Panel.

⇒ This study will include extensive tissue and blood samples for translational substudies aimed at understanding tumour biology and to identify potential prognostic and predictive biomarkers of clinical outcomes.

⇒ LUMOS-2 represents a successful international collaboration in a rare cancer between the Cooperative Trials Group for Neuro-Oncology, The University of Sydney and the Canadian Cancer Trials Group to facilitate wide-reaching patient accrual across Australia and Canada.

INTRODUCTION

The Central Brain Tumor Registry of the United States statistical report (2014–2018) showed the incidence rate for histologically grade 2 and grade 3 glioma is 0.53 per 100 000, with a median survival of 93 months.[1] These tumours are associated with mutations of the isocitrate dehydrogenase 1 (IDH1) and IDH 2 genes and have an improved prognosis[2–4] compared with glioblastoma patients. IDH mutation status is routinely assessed for diagnosis, prognosis and treatment planning. This study focuses on patients with histologically grade 2 or 3 IDH-mutant gliomas, excluding grade 4 IDH-mutant and IDH-wildtype gliomas due to their distinct biology and treatment paradigms.

There has been limited progress in the past three decades until the recent results showing the IDH inhibitor vorasidenib significantly improved progression-free survival (PFS) and delayed time to the next intervention in newly diagnosed IDH-mutant glioma patients post surgery.[5] Currently, there is limited access to this drug class worldwide pending regulatory approval or industry access schemes. Other commonly used treatments at diagnosis or progression include radiotherapy and alkylating chemotherapy, such as lomustine or temozolomide.[6] Lower-risk patients (age less than 40 years with gross tumour resection) sometimes have these treatments deferred after surgery to delay potential treatment-related neurotoxicity.[7] However, all grade 2/3 gliomas are incurable and at the time of inevitable relapse, there are limited treatment options and median survival is typically less than 12 months.[8 9] When feasible, resection at the time of progression is a common practice and is recommended in the United States National Comprehensive Cancer Network (NCCN) guidelines.[10] Clinical trials, if available to the patient, should be strongly considered due to the limited efficacy of available standard therapies.[6]

Low & Anaplastic Grade Glioma Umbrella Study of MOlecular Guided TherapieS (LUMOS-2) has been designed to provide patients with access to multiple drugs, with treatment selection based on the tumour's molecular profile, to maximise the possibility of benefit, with less toxicity. It represents a collaboration between international clinical trial groups, industry and government and not-for-profit funding bodies, to progress research and improve outcomes for grade 2/3 glioma patients at relapse. It continues the trend that accelerating progress for glioma patients requires strengthening multiple steps in the drug development process, including novel trial designs.[11]

METHODS AND ANALYSIS

Study design and rationale

LUMOS-2 will be an international, phase 2, multicentre, open-label, biomarker-directed, umbrella clinical trial for recurrent IDH mutant, histologically grade 2/3 glioma, including both astrocytoma and oligodendroglioma.[12] Funding was initially obtained for Australian sites, then subsequently for Canadian sites, using funding from local funding bodies. The study will open across Australia and Canada under the auspices of the Cooperative Trials Group for Neuro-Oncology (COGNO), The National Health and Medical Research Council (NHMRC) Clinical Trials Centre (CTC), The University of Sydney and the Canadian Cancer Trials Group (CCTG), respectively. The first patient was recruited to the study on 7 September 2023, and study recruitment for the first three arms is expected to be completed in 2025. Investigational products will be assigned, where possible, based on an identified molecular profile and administered until further disease progression or withdrawal for another reason. Pending further funding, additional therapeutic arms may be added to the LUMOS-2 umbrella to maximise the utility of the established study infrastructure.

This umbrella study will efficiently evaluate novel interventions for signals of efficacy and safety. By enabling the evaluation of multiple targets and subsequent patient referral for the best available therapy, this design maximises efficiency as compared with basket-type studies which only screen for one target and provide access to one drug, a design made even more challenging if screening for a molecular abnormality in a rare tumour type. An umbrella study takes participants in one disease group and allocates them to different treatments based on a strong biological rationale. By leveraging the efficiencies of this design, it is anticipated participants have access to multiple and more appropriate therapies, recruitment and evaluation of treatments will be faster, and pooled resourcing will result in cost benefits. Allocation to LUMOS-2 arms will be guided by a participant's molecular profile. Each country will use their own established pathways for molecular profiling by next-generation sequencing of gene panels. In Australia, molecular profiling will be provided via a pivotal collaboration with Omico, through the Molecular Screening and Therapeutics programme (MoST) or the Cancer Screening study (CaSP).[13] In Canada, profiling will be done through the Department of Paediatric Laboratory Medicine at the Hospital for Sick Children. Results of molecular profiling will be centrally reviewed by an international multidisciplinary Molecular Tumour Advisory Panel (MTAP) for guided treatment selection. Where the molecular profile supports assignment of a specific targeted agent, patients will be allocated to that agent within LUMOS-2. Where a potentially superior agent is available outside the trial, patients will be treated off-study at the discretion of their treating physician. All other patients will be randomised to arms where agents have multiple or non-targeted mechanisms of action using permuted blocks, stratified by glioma subclass (oligodendroglioma vs astrocytoma), and the study site. In the less likely event that a participant is identified as being suitable for multiple targeted agents, the MTAP will select the most suitable treatment option based on expert judgement.

At the time of on-study radiological progression, the participant will be referred to the LUMOS-2 Central

Review Committee for confirmation of progression, and also to determine whether re-resection and further tissue collection and rescreening for another arm of the LUMOS-2 study is appropriate. It is anticipated that 50% of participants will undergo a further craniotomy and tissue collection. This novel feature of LUMOS-2 acknowledges that there are likely to be limited other options for these patients, who are often young and well, and also allows for the important translational research into the mechanisms of resistance and associated biomarkers. There is also no evidence to suggest that any of the arms are likely to show cross-resistance or to impact the outcomes of each other with sequential treatment.

Importantly, LUMOS-2 molecular profiling will require the analysis of contemporaneous tumour tissue, that is, tissue obtained from craniotomy at recurrence rather than archival diagnostic tissue. There are several advantages to obtaining contemporaneous tumour tissue for molecular profiling. First, it is essential to confirm that imaging changes associated with disease recurrence represent true tumour recurrence. Second, data from our group[14] and others[15] have shown that tumours mutate significantly over time, especially after treatment. Having an accurate molecular profile of the tumour at the time of treatment selection is often essential for targeted agents, where therapeutic benefit may be reliant on the presence of a molecular biomarker. Targeted agents may also have better tolerability compared with chemotherapy based on their selectivity for the tumour cells. Furthermore, it is anticipated that using the LUMOS-2 umbrella design will facilitate and accelerate evaluation of new drugs or currently available drugs in a new indication for signals of efficacy, hastening the translation of therapies to the clinical setting.

Rationale for the therapies

Intervention 1: paxalisib

Activating and transforming mutations, as well as amplification, in the p110α subunit of phosphatidylinositol-3 kinase (PI3K) are commonly found in solid and haematologic tumours. In addition, the PI3K/Akt pathway is activated in several cancer types by receptor tyrosine kinase signalling, or loss of phosphatase and tensin homolog (PTEN) expression or function. These mechanisms of pathway activation are observed in more than 70% of glioblastomas.[16] IDH-mutant diffuse gliomas have active PI3K/AKT/mammalian target of rapamycin (mTOR) signalling in 21.7% and 56.6% of cases as determined by genetic and protein evaluations, respectively.[17] Paxalisib is a brain-penetrant and selective inhibitor of class I PI3K and mTOR, which has proved efficacious in non-clinical models of brain tumours driven by activation of the PI3K pathway.[18] Paxalisib inhibits proliferation of glioma cell lines in vitro and inhibits tumour growth in intracranial and subcutaneous mouse xenograft models of human glioblastoma.[19] For paxalisib and the other agents in this trial, preclinical data are limited due to the problems of representative IDH-mutant preclinical models and hence inclusion in LUMOS-2 is based on data from glioblastoma or other preclinical rationale. These results support evaluation of paxalisib, currently not approved for any indication, as a potential therapeutic agent for brain cancer and will be recommended in this study for patients with genomic alterations likely to be responsive to PI3K inhibition. Potential cardiac effects will necessitate exclusion of participants whose baseline QTc interval is greater than 470 ms or those with clinically significant cardiac history such as myocardial infarction, symptomatic bradycardia, active congestive heart failure or angina pectoris. A daily oral dose of 45 mg, escalating to 60 mg daily if tolerated is supported by clinical studies.[20]

Intervention 2: cadonilimab

A potential benefit of immunotherapy is to provide improved, longer-term efficacy by enhancing the patient's own immune response against the tumour. Cadonilimab (AK104) is a humanised, biospecific immunoglobulin monoclonal antibody (mAb) that binds to programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) coexpressed on tumour-infiltrating lymphocytes (TILs) with high affinity, achieving its cotargeting efficacy.[21] Dual PD-1 and CTLA-4 engagement has downstream immunomodulator effects on cytokine production, proliferation, cell survival and transcription factors associated with effector T cell function. Inhibition of this process via cadonilimab provides a rationale for its investigation as an anticancer immunotherapy agent. Immune checkpoint blockade using anti-PD-1 mAb (nivolumab) in recurrent glioblastoma did not improve median overall survival (OS) compared with bevacizumab.[22] However, promising results using an anti-PD-1 mAb (pembrolizumab) given as a neoadjuvant drug to patients with recurrent GBM was associated with PD-1 blockade, enhancing the local and systemic antitumour immune response, associated with a clinically meaningful outcome of median OS of 13.7 months.[23] Targeting both CTLA-4 and PD-1 pathways using cadonilimab may provide additive or synergistic activity.[24] Cadonilimab has been approved in China in patients with relapsed or metastatic cervical cancer who have progressed on, or after platinum-based chemotherapy.[25] Although there are expectations of a manageable safety profile, immune-related adverse events (AEs) are a potential safety risk for all immunotherapies and AEs will be monitored up to 90 days after the last treatment dose.

Intervention 3: selinexor

Selinexor is a selective inhibitor of nuclear export, which binds to exportin 1 (XPO1) shutting down its nuclear export activity. Neoplasms require nuclear export of tumour suppressor proteins, oncoprotein mRNA and glucocorticoid receptor (GR) to stimulate uncontrolled tumour growth,[26] the corollary being blockade of this pathway will counteract carcinogenic pathways and inhibit cancer growth. Approval has been granted in several countries around the world, including Australia

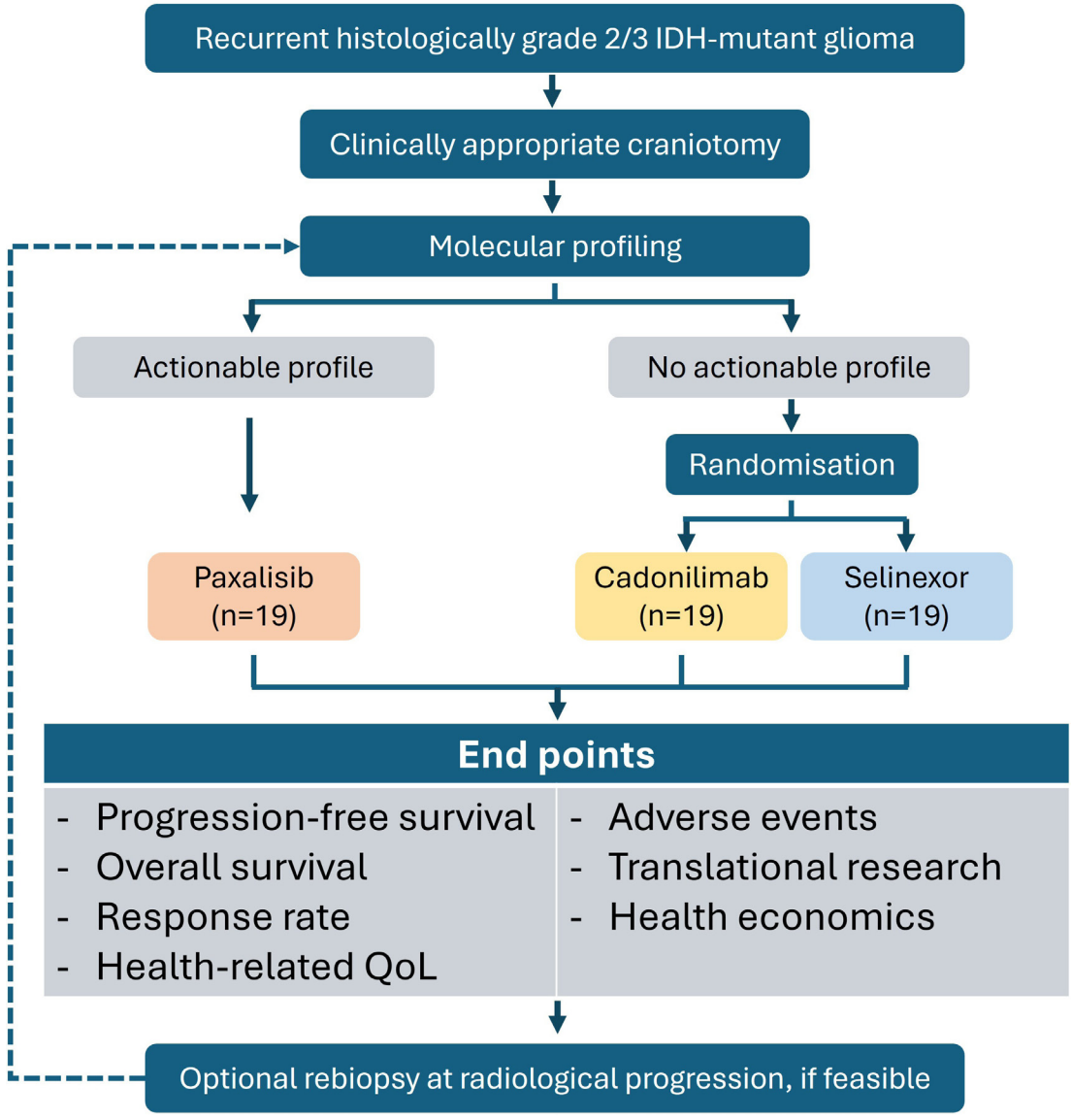

Figure 1 LUMOS2: Study schema. IDH, isocitrate dehydrogenase; LUMOS-2, Low & Anaplastic Grade Glioma Umbrella Study of MOlecular Guided TherapieS; QOL, quality of life.

and the USA for haematological cancer indications. Considering selinexor's demonstrated broad antitumour activity, it provides a strong rationale to evaluate selinexor in solid brain tumours in the current umbrella trial. Preclinical studies have demonstrated antitumour activity of selinexor as monotherapy and in combination with a broad array of drugs in solid tumour mouse models.[27–29] A phase II study of the efficacy and safety of selinexor in recurrent glioblastoma showed clinically relevant 6-month PFS with manageable side effects.[30]

Participants

Recruitment targets are anticipated to be met through a process aimed at identifying patients by direct referrals from the neuro-oncology multidisciplinary team. Participants will be approached directly by the investigator or by a delegated member of their clinical team to assess suitability and obtain participant consent for the study. The participant journey is described in the study schema shown in figure 1. Participant enrolment is a staged process. In the first stage, eligible adults identified per the inclusion and exclusion criteria listed in box 1 will undergo tumour resection and molecular profiling, followed by a LUMOS-2 treatment arm recommendation. Participants and their study physicians will undertake a second screening process for the proposed treatment arm to ensure participants are suitable per the inclusion and exclusion criteria for a treatment arm as listed in box 2. In consultation with their study physician, participants may elect to follow the treatment recommendation and partake in a LUMOS-2 therapeutic arm or decide to return to the care of their treating physician and receive treatment outside of the trial. LUMOS-2 participants will be treated until there is progression of disease, excessive toxicity that cannot be adequately managed or withdrawal for another reason. Every effort will be made to maintain contact with participants for the duration of the study via

Box 1

Key inclusion criteria—molecular profiling

1. Adults, aged 18 years and older.
2. Histologically confirmed glioma, isocitrate dehydrogenase (IDH)-mutant, histologically grade 2 or 3 at initial diagnosis (ie, without necrosis or microvascular proliferation); including *CDKN2A/B* homozygous deleted IDH-mutant astrocytomas but not IDH-wild-type diffuse astrocytoma with any of *TERT* promoter mutation, *EGFR* amplification and/or +7/–10 copy number changes (ie, molecular features of glioblastoma).
3. Evidence of disease progression post radiotherapy and chemotherapy as per response assessment in neuro-oncology criteria 2.0 (most notably a 25% increase in T2/FLAIR area, a 25% increase in existing enhancing disease and/or a new measurable enhancing disease); with a clinical indication for neurosurgery.
4. Prior treatment with CNS radiotherapy and alkylating chemotherapy, defined as either sequential therapy with CNS radiotherapy then an alkylating agent, or concurrent CNS radiotherapy with an alkylating agent.
5. ECOG performance status 0–2.
6. Willing and able to comply with all study requirements, including treatment, timing and/or nature of required assessments. It is the intention that molecular profiling is performed for patients who are in principle wishing to take part in a treatment arm if they are found to be eligible following molecular profiling.
7. Signed, written informed consent for Low & Anaplastic Grade Glioma Umbrella Study of MOlecular Guided TherapieS molecular profiling, and linkage to healthcare resource and medication usage records (Medical Benefits Schedule and Pharmaceutical Benefits Scheme) for Australian participants.

Key exclusion criteria—molecular profiling

1. Prior treatment with bevacizumab
2. Intrasurgical treatments (eg, oncolytic virus administration, Gliadel wafers) at their last craniotomy prior to study enrolment.
3. Comorbidities or conditions (eg, psychiatric) that may compromise assessment of key outcomes or in the opinion of the physician limit the ability of the participant to comply with the protocol.
4. Unable (eg, due to pacemaker or ICD device) or unwilling to have a contrast-enhanced MRI of the head.
5. Any unresolved toxicity (>Common Terminology Criteria for Adverse Events grade 2) from previous anticancer therapy (those with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included eg, hearing loss, peripheral neuropathy).
6. Pregnancy, lactation, or inadequate contraception.

Box 2 Inclusion and exclusion criteria—treatment arm

The study's treatment component requires the following inclusion and exclusion criteria to be met, with the caveat there may be additional treatment-specific inclusion and exclusion criteria.

Key inclusion criteria—study treatment

⇒ Adequate recovery from surgery in the opinion of the treating physician (as evidenced by ECOG performance status 0–2).
⇒ Adequate organ system function postsurgery as assessed by the following minimal laboratory requirements (within 7 days prior to first administration of study drug).
⇒ Bone marrow function; platelets≥100×10^9/L, ANC≥1.5×10^9/L and haemoglobin≥90 g/L (5.6 mmol/L).
⇒ Liver function; ALT/AST≤3×ULN and total bilirubin≤1.5×ULN.
⇒ Renal function; serum creatinine≤1.5×ULN.
⇒ Low & Anaplastic Grade Glioma Umbrella Study of MOlecular Guided TherapieS (LUMOS-2) Molecular Tumour Advisory Panel report confirming eligibility to this treatment arm.
⇒ Willing and able to comply with all study requirements, including treatment, timing and/or nature of required assessments.
⇒ Signed, written informed consent for a LUMOS-2 treatment arm.

Key exclusion criteria—study treatment

⇒ Intrasurgical treatments (eg, oncolytic virus administration, Gliadel wafers) at their last craniotomy prior to study enrolment.
⇒ Presence of any metastatic tumours at the time of craniotomy that is not consistent with original glioma diagnosis.
⇒ Prior isocitrate dehydrogenase inhibitor therapy within 4 weeks of first dose of LUMOS-2 investigational treatment.
⇒ Prior investigational agents within 4 weeks of first dose of LUMOS-2 investigational treatment.
⇒ Concomitant medications may interact with the investigational product(s) in the opinion of the physician.
⇒ Pregnancy, lactation or inadequate contraception.

phone and email. Participants who cease investigational product prior to the time recommended in the protocol will be requested to continue follow-up visits according to the protocol and will be included in the intention-to-treat analysis. At progression, while on study, if appropriate, participants may undergo re-resection and be rescreened for another treatment arm of the LUMOS-2 study.

Study hypothesis, aims, objectives and related outcomes

Primary aim: To evaluate the clinical activity of targeted and other novel treatments for recurrent IDH mutant, histologically grade 2/3 glioma.

The hypothesis is patients with recurrent IDH mutant, histologically grade 2/3 gliomas, selected according to molecular alterations, will benefit from treatment with targeted agents allocated according to molecular tumour board recommendations, or treatment with agents with other novel but pleiotropic mechanisms of actions.

Primary objective and outcome

Clinical benefit will be primarily evaluated by PFS at 6 months (PFS6). PFS is defined as the time after study enrolment (on the participants most recent treatment allocation) to disease progression, as measured by conventional contrast-enhanced MRI and evaluated according to response assessment in neuro-oncology criteria 2.0 (RANO 2.0),[31] or death from any cause. Participants alive and progression-free will be censored at the date of their last known status. PFS6 will be estimated using the Kaplan-Meier method. PFS6 was selected as the primary endpoint based on available historical data and its role as a pragmatic surrogate for OS in neuro-oncology trials. It is particularly appropriate for this study, which allows patient re-entry after progression through repeat biopsy and molecular reprofiling, making OS less suitable. Including both progression and death as events aligns

with regulatory standards, avoids bias from censoring deaths before progression can be assessed, and provides a comprehensive measure of treatment effectiveness in a context with minimal competing risks.

Secondary aim: To further evaluate the clinical safety of targeted and other novel treatments for recurrent IDH mutant, histologically grade 2/3 glioma.

The hypothesis is that tailoring treatments to individuals will maximise benefits relative to side effects, resulting in a superior therapeutic ratio.

Secondary objectives and outcomes

- Evaluation of clinical efficacy will also be determined by
  1. OS is defined as the interval from date of study enrolment (on the participant's most recent treatment allocation) to date of death from any cause or the date of last known follow-up alive.
  2. Overall response rate of the assigned intervention is defined as either a complete response or partial response as measured by conventional contrast-enhanced MRI and evaluated according to RANO 2.0.[31]
- Safety and tolerability of each intervention will also be determined by
  1. AE reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 to classify and grade the severity of AEs.[32]
  2. Health-related Quality of Life Questionnaires (QLQ) completed by participants, specifically the EORTC core QLQ (QLQ-C30) and brain cancer-specific module (BN-20), to help assess the balance between efficacy and toxicity.

Exploratory aims 1: to obtain information on healthcare resource use

Of particular interest is whether there is additional value to a targeted treatment approach, incorporating molecular profiling and therapy selection, relative to current standard of care. This will be considered within an exploratory economic evaluation for Australian participants.

Exploratory aims 2: to identify potential biomarkers that are prognostic and/or predictive of clinical endpoints

Translational research will explore biomarkers associated with clinical endpoints including PFS6, OS, response rate, treatment sensitivity and resistance and to better understand the biology of recurrent grade 2/3, IDH-mutant glioma. Since the identification of new biomarkers that correlate with disease activity (prognosis), treatment efficacy or safety is rapidly evolving, the definitive list of biomarkers will be guided by emerging data over the course of the study.

Schedule of assessments

At baseline, demographic information and medical history will be collected including year of birth, sex, weight, height, self-reported ethnicity and past anticancer treatments. A clinical assessment at baseline, before every treatment, at end of treatment (EOT) on study, and 28 days post-EOT will be undertaken. Clinical assessment will include a pregnancy test (at baseline and then if applicable), routine blood tests for organ function, physical examination, performance status, weight and vital signs. A contrast-enhanced MRI will be collected within 28 days prior to the on-study craniotomy to demonstrate evidence of recurrent disease, as required for study eligibility. An MRI within 2 weeks prior to study treatment is required for a baseline scan, and then 8 weekly from the date of first treatment until recurrent disease. Patient-reported outcomes are collected at baseline and then before every treatment until disease progression. After discontinuing study treatment, participants will be followed up for toxicity for at least 28 days (90 days following discontinuation for any investigational immunotherapy treatment). Participants will be followed up for survival at 12 weekly intervals post EOT.

Study treatments will be administered according to the administration schedule for each intervention (table 1).

Table 1 Study intervention schedule

Drug intervention	Dose	Route	Concomitant care—recommended or prohibited
Paxalisib	45 mg once daily on days 1–28 of a 28-day cycle for cycle 1, escalating to 60 mg daily if tolerated.	Oral	Recommended: Alcohol-free dexamethasone 0.5 mg/5 mL oral solution.
Cadonilimab	6 mg/kg every 2 weeks in a 28-day cycle.	Intravenous Infusion	Prohibited: corticosteroids or other immunosuppressive medications. Additional immunotherapy, cytotoxic chemotherapy, antiangiogenic agents (eg, bevacizumab), radiotherapy or other investigational agents.
Selinexor	80 mg weekly in a 28-day cycle	Oral	Recommended: ondansetron at a dosage of 8 mg three times daily for a few days after each treatment, and olanzapine at a daily oral dose of 2.5 mg for 2 months.

Participant safety is the site investigator's primary responsibility; thus, their discretion should determine the course of action for the management of toxicities. In general, the investigational product should be withheld during AEs of severity grade 3–4 (according to the US National Cancer Institute Common Terminology Criteria for Adverse Events 5.0) and not restarted until the AE has resolved to grade 0–1, at the site investigator's discretion. Participants receiving oral medications will be asked to return unused and empty drug containers at each return visit to ensure compliance.

This protocol is written following the Standard Protocol Items: Recommendations for Interventional Trials Recommendations for Interventional Trials statement.[33]

Imaging

Measurable disease at baseline and response assessment will be defined according to RANO 2.0.[31]

Translational research

Serial tissue (archival diagnostic, at surgery, at any relapse where available) and blood biospecimens (at molecular screening, cycle 1 day 1, at MRI (week 8) and EOT) will be collected for translational research studies to explore potential biomarkers that are prognostic and/or predictive of clinical endpoints. Biospecimens may also include intraoperative cavitating ultrasound aspirator fluid and peripheral blood mononuclear cells at selected hospital sites. Translational research will be tailored to each treatment arm as appropriate and will be guided by future developments in this field.

Health economic evaluation

The use of molecular profiling in LUMOS-2 to guide treatment selection—via various pathways depending on whether actionable mutations are present or not—represents a novel approach to the treatment of IDH mutant grade 2/3 glioma in Australia and Canada. Of particular interest is whether there is additional economic value to that targeted treatment approach, incorporating molecular profiling and therapy selection, in these patients relative to current standard of care. This will be considered within an exploratory economic evaluation that will assess the costs and consequences (expressed in terms of quality-adjusted life-years) of the targeted approach to care in LUMOS-2 and use those outputs in a subsequent analysis to investigate the potential cost-effectiveness relative to the current standard of care in grade 2/3 glioma.

Statistical methods

Each treatment arm aims to recruit 19 participants. Prior studies in similar populations have shown 6-month PFS of approximately 36% (range 30%–40%),[34 35] which will serve as our historical benchmark for assessing clinical benefit, and a rate lower than this would not be considered worthwhile. Nineteen participants per arm have 80% power at 5% one-sided alpha to rule out a rate of 36% if the true rate is 65%, using a one-sample exact binomial test, and will allow estimation of 6-month PFS with a 95% CI of maximum width±21%. While this design lacks the precision of larger trials, it is tailored to detect an indicative signal of activity, recognising that larger sample sizes are neither feasible nor appropriate for a phase 2 study of a rare cancer. Analysis of all treatment arms will follow similar principles and any differences will be described in a detailed statistical analysis plan, which will be finalised prior to the analysis of any treatment arm. This approach aligns with our standard operating procedures and ensures that all statistical considerations are clearly documented while maintaining flexibility to address treatment arm-specific nuances. Statistical analysis will be conducted by the Biostatistics Department of the NHMRC CTC.

The primary outcome of 6 months PFS after study enrolment (on the participant's most recent treatment allocation) will be calculated using the Kaplan-Meier method, which accounts for censoring and provides unbiased survival estimates by incorporating the time each participant contributes up to progression, death or censoring. Results will be presented with a one-sided 95% CI (using the lower bound), and clinical benefit will be assessed by determining whether the lower bound exceeds the prespecified historical benchmark of 36%. Participant characteristics, treatment details and other study outcomes will be presented using standard descriptive statistics. There is no plan for statistical comparisons within or between arms; however, results may be tabulated for different participant groups within and across arms, and in some circumstances, data from different arms may be combined for comparisons. This is because the primary aim of this phase 2 study is to detect an indicative signal of activity within each arm, with promising treatments later advancing to larger comparative studies. Due to the limited sample size, adjustments for centre-level variability are not feasible. If sufficient data are available, proportional hazards regression models will be used to explore predictors of outcome. The primary endpoint of PFS6 is assessed at a single time point, avoiding the need for repeated measures analysis.

Data management

The data controller for the study will be The University of Sydney. The study will be conducted in accordance with applicable Privacy Acts and Regulations in each country where the study is conducted. A data management plan will be implemented, and all information required for monitoring and analysis of the study will be stored securely in the Medidata Clinical Cloud. Medidata has ISO 27018 certification for protecting Personally Identifiable Information in the cloud. Study data will be regularly monitored for protocol compliance, data accuracy and completeness centrally/remotely and/or onsite by the sponsor or their delegates, in accordance with the study's monitoring plan.

Sponsor and insurance

The University of Sydney, as sponsor of the study in Australia, and the CCTG, as local sponsor in Canada, have

insurance arrangements sufficient to cover its sponsor-related liabilities associated with the study. This insurance policy is in accordance with local laws and requirements.

Trial governance

LUMOS-2 will be an international collaboration between COGNO, and the NHMRC CTC, The University of Sydney, and the CCTG to facilitate wide-reaching patient accrual across Australia and Canada. In addition, LUMOS-2 has partnered with Omico Australia to provide the integral molecular profiling via Omico's government-backed precision medicine networks. Sponsored by the University of Sydney, and in Canada by the CCTG, this study will be performed in accordance with the Integrated Addendum to International Conference on Harmonisation (ICH) E6 (R1): Guideline for Good Clinical Practice ICH E6(R2) annotated with Australian Therapeutic Goods Administration comments and in compliance with applicable laws and regulations, NHMRC Statement on Ethical Conduct in Research Involving Humans (2018), NHMRC Australian Code for the Responsible Conduct of Research (2018) and principles laid down by the World Medical Assembly in the Declaration of Helsinki 2013. The study will be conducted in accordance with applicable Privacy Acts and Regulations and other relevant ethical and regulatory directives within each country where the study operates. All data generated in this study will remain confidential. All information will be stored securely at the NHMRC CTC, The University of Sydney. A TMC has been convened by the sponsor and will operate in accordance with the TMC charter. This TMC charter describes the committee's structure, roles and responsibilities, including their remit to oversee the study planning and management on an international level. An Independent Data Monitoring Committee (IDMC) will meet at least 6 monthly to review patient safety and trial progress. The IDMC will make recommendations to the TMC regarding study continuation and participant safety. A translational research committee will advise on the translational research components of the study.

Patient and public involvement

A Consumer and Community Advisory Panel (CAP) has been convened to provide consumer perspective and input on consumer engagement for the LUMOS-2 study, as well as provide valuable connections with the target population to assist in educating and informing the community on trial activities relevant to them. A CAP representative will be a member of the TMC and provide regular updates to the CAP on the LUMOS-2 study.

Informed consent

All participants will be informed of the study's objectives, potential side effects of the procedures and interventions, who has access to their information, and any compensation provisions for individuals who experience harm because of trial participation. It will be emphasised that participation is voluntary and that the patient is allowed to refuse further participation at any time. This will not prejudice the patient's subsequent care. There are four informed consent documents required for LUMOS-2 (online supplemental files 1–4).

- A general LUMOS-2 study consent prior to craniotomy.
- Molecular profiling programme consent for molecular testing of tumour tissue via the MoST or CaSP programme in Australia and as a trial-specific process in Canada.
- A treatment-specific consent form after allocation/randomisation to a treatment arm.
- For Australian participants, consent for linkage to MBS and PBS records for health economics outcomes.

ETHICS AND DISSEMINATION

Central ethics approval was obtained from the Sydney Local Health District Ethics Review Committee, Royal Prince Alfred Hospital Zone, Sydney, Australia (Approval: 2022/ETH02230). Any modifications to the protocol which may impact the conduct of the study, potential benefit of the participant, or may affect participant safety, including changes in core objectives, design, participant population, procedures or significant administrative aspects will require a formal amendment to the protocol. Such amendments will be agreed on by the TMC and approved by the relevant ethics committee prior to implementation and notified to the health authorities in accordance with local regulations. Other clinical sites will provide oversight through local governance processes, including obtaining informed consent from suitable participants. A report describing the results of the study will be submitted to international meetings and peer-reviewed journals. A deidentified summary of the results will be published and shared together with the publication of the study results for investigators to share and discuss with study participants. Coauthorship will be based on standard International Committee of Medical Journal Editors guidelines. This study data set is registered through ANZCTR Trial Registration ACTRN12623000096651, searchable via the WHO International Clinical Trials Registry, prospectively registered on 27 January 2023.

DISCUSSION

The LUMOS-2 trial implements an innovative trial design for drug testing and scientific research in patients with relapsed histologically grade 2/3 gliomas. It will use a precision oncology approach to simultaneously address several key barriers in this patient population. First, it postulates that tailoring treatments to individuals will maximise benefits and limit side effects compared with chemotherapy. While recognising that biomarkers are often yet to be fully validated for clinical use, particularly with emerging drugs, we still anticipate that a sophisticated and multidisciplinary MTAP can enrich patients more likely to respond to a targeted agent with a strong scientific rationale. Even if we subsequently show that the specified biomarker is not of clinical utility, our systematic

collection of tissue at study entry, with a strong emphasis on obtaining tissue at relapse as well, will allow investigation of alternative biomarkers of sensitivity to these anticancer agents. Second, the use of an umbrella design with comprehensive molecular profiling at study entry, coupled with access to a range of drugs, aims to address the inefficiencies associated with undertaking individual studies with low prevalence mutations/treatment targets in a population with relatively small absolute numbers.

We have previously shown that this approach was possible despite its novel and ambitious scope. The LUMOS pilot study was an Australian multicentre study that established a multicentre, multistate group of hospitals to test whether recently acquired formalin-fixed paraffin-embedded tissue (within 6 months of molecular profiling) could be used for molecular profiling with an acceptable turn-around time for clinical use. This pilot study confirmed the ability to rapidly obtain and molecularly profile tumour tissue in this patient population with a median turnaround time of 6.2 weeks. There was an average of 2.2 actionable mutations per patient, with all patients having at least one actionable mutation.[36] Although the LUMOS pilot design did not include any on-treatment arms, two patients were able to access relevant targeted agents outside the study. Building on this established infrastructure and methodology of the LUMOS pilot study, LUMOS-2 expanded the footprint of the network to include additional sites across Australia and formally included three treatments arms for patients. Furthermore, the expansion of LUMOS-2 to international partners in Canada underscores the attractive features of the trial and facilitates recruitment to what is still a niche group of tumours. This ambitious undertaking across Australia and Canada, involving multiple pharmaceutical and molecular testing partners, will facilitate broad access to clinical trials and establish enduring infrastructure for a glioma precision medicine approach.

While LUMOS-2 will begin with three interventional arms, we already have mature plans to add additional arms, with enthusiastic support from funding bodies and industry partners. We will work to add further arms as funding and drug access allow. While our current focus is on testing monotherapy drug regimens, future arms may encompass combination therapies and non-drug interventions within the versatile framework of an umbrella study. Lastly, there has been substantial interest from investigators in other countries and work to expand LUMOS-2 globally is underway.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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