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CLINICAL TRIAL PROTOCOL



# A perioperative study of Safusidenib in patients with *IDH1*-mutated glioma

Sarah A Cain[a], Monique Topp[b], Mark Rosenthal[b], Robert Tobler[c], Saskia Freytag[c,d], Sarah A Best[c,d], James R Whittle[*,‡,b,c,d] and Katharine J Drummond[**,‡,a,e]

[a]Department of Neurosurgery, Royal Melbourne Hospital, Parkville, 3052, Australia; [b]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, 3000, Australia; [c]Personalised Oncology Division, The Walter & Eliza Hall Institute of Medical Research, Parkville, 3052, Australia; [d]Department of Medical Biology, University of Melbourne, Parkville, 3052, Australia; [e]Department of Surgery (Royal Melbourne Hospital), Melbourne Medical School, Faculty of Medicine, Dentistry & Health Sciences, The University of Melbourne, Parkville, 3052, Australia

**ABSTRACT**

This is a single arm, open label perioperative trial to assess the feasibility, pharmacokinetics and pharmacodynamics of treatment with safusidenib following biopsy, and prior to surgical resection in patients with *IDH1* mutated glioma who have not received radiation therapy or chemotherapy. Fifteen participants will receive treatment in two parts. First, biopsy followed by one cycle (28 days) of safusidenib, an orally available, small molecular inhibitor of mutated IDH1, then maximal safe resection of the tumor (Part A). Second, after recovery from surgery, safusidenib until disease progression or unacceptable toxicity (Part B). This research will enable objective measurement of biological activity of safusidenib in patients with *IDH1* mutated glioma. Anti-tumor activity will be assessed by progression free survival and time to next intervention.

**Clinical Trial Registration:** NCT05577416 (ClinicalTrials.gov)

**Plain language summary:** Adult low-grade gliomas (aLGG) are primary brain cancers, defined by mutations in *IDH1* or *IDH2*. When the *IDH* gene becomes abnormal (mutated), production of a metabolite that causes cancer cells to grow is increased. These tumors grow slowly but invade the normal functioning brain, making them nearly impossible to cure. The current standard of care treatment includes surgery, followed by radiation therapy and chemotherapy, the timing of which depends on the risk of cancer regrowth. Some patients may be suitable for monitoring with MRI scans alone, however recurrences will inevitably occur. Recently developed targeted mutant IDH inhibitors for aLGG patients may be beneficial both at diagnosis and recurrence. Notably, early treatment prior to radiation therapy and chemotherapy delays growth of aLGG and the need for subsequent radiation therapy and chemotherapy. Nevertheless, most patients will eventually suffer further tumor growth and the optimal timing and sequencing of these therapies remains an area of active research. This research investigates the mutant *I*DH1 inhibitor safusidenib. The researchers are conducting an innovative clinical trial where patients with aLGG, who have not received radiation therapy or chemotherapy, are treated with safusidenib following a biopsy and prior to surgical removal of their tumor. In this study they investigate whether this trial design is safe and feasible, and how safusidenib works; with the goal to better understand the optimal use of IDH inhibitors for patients with aLGG.

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AB-218; isocitrate dehydrogenase 1; IDH1; low grade glioma; Phase 0; safusidenib; window of opportunity

## 1. Introduction

### 1.1. Background & rationale

The incidence of primary malignant brain tumors is approximately 7 per 100,000 individuals, of which 30% are diffusely infiltrating lower-grade (WHO grade 2) gliomas [1]. Adult low-grade gliomas (aLGG) are defined by mutations in *IDH1* or *IDH2* and grow slowly with a diffusely infiltrative pattern that makes them near impossible to cure [2]. The natural history tends toward malignant progression with survival rates ranging between 2 and 15 years [3,4]. Recurrences will almost inevitably occur, despite multi-modality treatment that includes surgery, radiation therapy and chemotherapy. Tragically, aLGG usually affects younger patients, causing enormous loss of potential years of life and cost to the commu-

**CONTACT** James R Whittle jim.whittle@petermac.org; Katharine J Drummond kate.drummond@mh.org.au
‡These authors jointly supervised this work

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nity [5]. Understandably, most research has focused on WHO grade 4 glioma (glioblastoma [GBM]) which is the most common malignant brain cancer in adults. Thus, patients with aLGG have historically been neglected in clinical trials. The recent emergence of targeted mutant IDH inhibitors [6–9] has significantly changed this landscape with efforts now focused on identifying prognostic markers, new treatment paradigms and future combination studies [10].

### 1.2. Isocitrate dehydrogenase mutations in glioma

The WHO CNS 5th Edition (CNS5) [11] has consolidated the role of molecular biomarkers in brain tumor classification. Adult gliomas are classified by *IDH* mutation status, with *IDH* wildtype gliomas designated WHO grade 4 GBM and *IDH* mutations defining oligodendrogliomas and astrocytomas. Historically, *IDH* mutations were found in 12% of then classified secondary glioblastomas [12] and subsequently described in >70% of patients with aLGG [13], highlighting the epidemiological and prognostic impact of *IDH* mutations. Oligodendrogliomas are further defined by 1p/19q codeletions. The WHO CNS5 employs *within-tumor-type* grading, with oligodendrogliomas graded 2–3 and astrocytomas graded 2–4 [11]. This study focuses on *IDH1* mutated WHO grade 2 low grade gliomas.

While normal IDH1 catalyzes the oxidative decarboxylation of isocitrate to $\alpha$-KG, mutated IDH1 gains neomorphic activity converting $\alpha$-KG to 2-HG [14]. 2-HG is an oncometabolite with pleotropic effects on tumorigenesis, including hypermethylation of histones and DNA [15] and suppression of normal cellular differentiation (Figure 1) [16]. Excess production of 2-HG outcompetes $\alpha$-KG, inhibiting $\alpha$-KG-dependent enzymes involved in epigenetic regulation, collagen synthesis and cell signaling, leading to a block in differentiation of progenitor cells and subsequent development of cancer [17,18]. Therefore, inhibition of mutated IDH1 and the concomitant decrease in 2-HG production may restore cellular differentiation, providing therapeutic benefit in *IDH1*-mutated cancers. In addition, 2-HG promotes an immunosuppressive tumor microenvironment through the inhibition of $CD8^+$ T-cells [19,20], and contributes to tumorigenesis through oxidative damage by disrupted redox signaling [16] and increased angiogenesis via hydroxylation of HIF1$\alpha$ mediated by PHD enzymes [21,22].

*IDH* mutations are an early event in gliomagenesis and remain important throughout the tumor life cycle, with ubiquitous expression and almost universal retention during the disease course [23,24]. The development of *IDH* mutant gliomas is likely a multistep process, with *IDH* mutations followed by acquisition of further mutations and increasing aggressiveness [25]. 2-HG likely becomes dispensable once an oncogenic program has been established with implications regarding the appropriate window of opportunity for the application of mutant IDH inhibitors [26].

### 1.3. Current treatment

Currently, newly diagnosed aLGG are treated with maximal safe surgical resection, followed by adjuvant therapy, with timing based on risk assessment. There is accumulating evidence that reduced tumor volume will improve long-term survival and quality of life [27]. The role of surgery cannot ethically be investigated in a randomised clinical trial, however in retrospective case series [28–33] and a cohort study comparing surgical strategies, early more extensive surgery has been associated with improved overall survival [34]. However, the selection bias of these retrospective studies limits utility. Moreover, prior studies were based on inferior standard morphological histopathological diagnosis, without advanced molecular classification.

More recent analysis of surgery for patients with aLGG and molecular analysis supports maximal safe resection as first-line treatment [35]. In addition, repeat craniotomy and safe resection at the time of disease recurrence or progression is feasible in most patients providing survival benefits [36,37], of whom up to 50% achieve a gross total resection [31]. Thus, the standard of care is moving to aggressive safe early resection with mounting evidence of survival benefit. In all series since 2005 with objective postoperative evaluation of extent of resection on MRI, a more aggressive resection predicted improvement in overall survival compared with simple debulking or biopsy [2].

In the RTOG9802 study, patients with WHO grade 2 glioma at high risk of recurrence (age >40 years and/or ongoing neurological symptoms, or age 18–39 and undergone biopsy or subtotal resection only) benefited from post-radiation chemotherapy [38]. Thus, radiation therapy with sequential chemotherapy has become standard of care for patients with *IDH* mutant grade 2 gliomas who are at high risk for progression [38], however, there is less evidence for optimal timing for treatment [10].

Some patients with *IDH* mutant grade 2 gliomas may be suitable for active surveillance with regular MRI scans rather than immediate adjuvant radiation therapy followed by chemotherapy after diagnosis. This active surveillance period provides an opportunity for the evaluation of new therapies with the potential to postpone the long-term side effects of adjuvant treat-

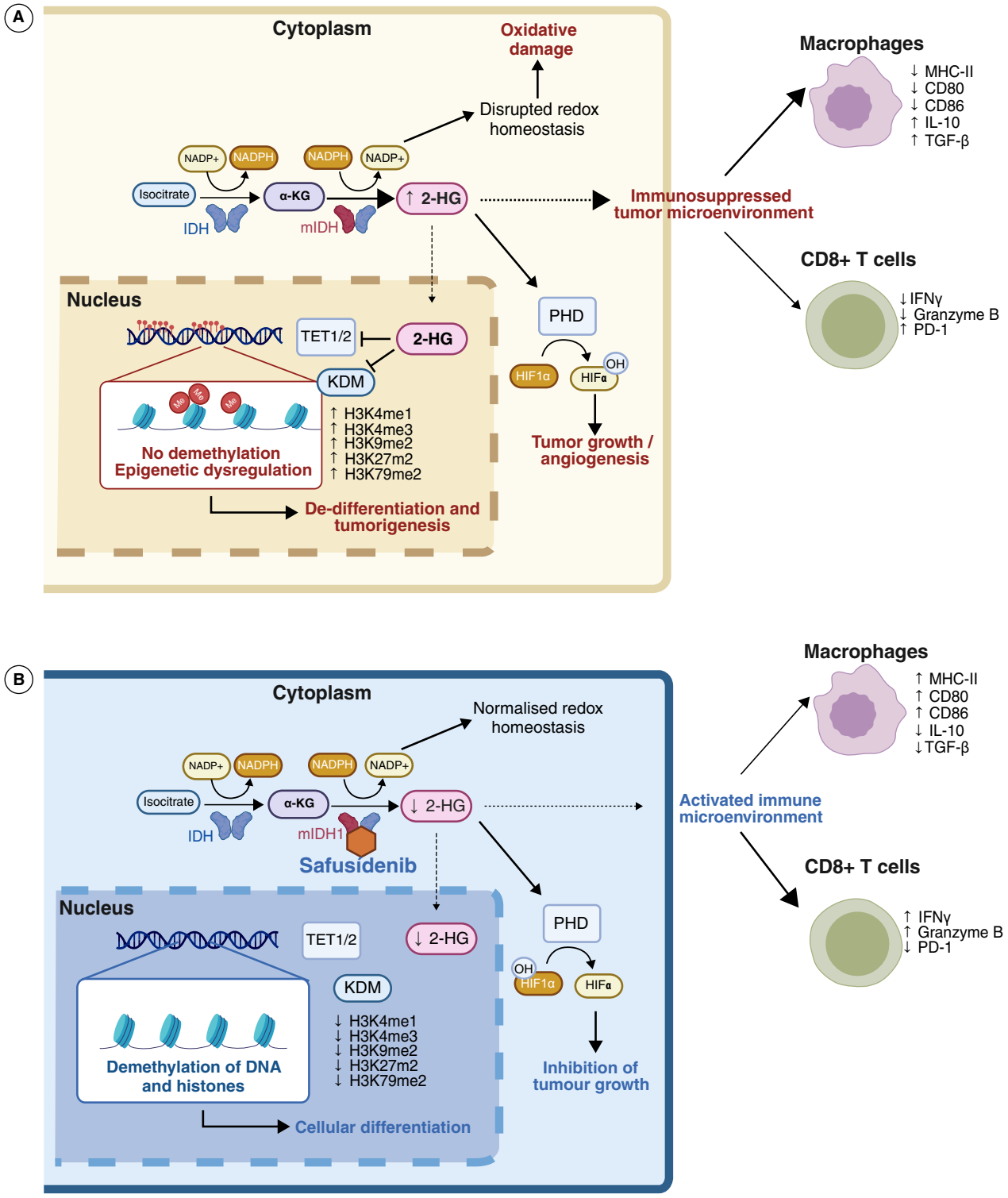


Figure 1. *IDH* mutations and mutant IDH inhibitors. **(A)** Mutations in *IDH1* and *IDH2* increase 2-HG promoting pleotropic effects leading to tumorigenesis. 2-HG competitively inhibits $\alpha$-KG binding to histone demethylases, including KDM2A, TET1 and TET2 hydroxymethylases promoting epigenetic dysregulation through hypermethylation of DNA. 2-HG also stabilises HIF1$\alpha$ promoting increased vascular endothelial growth factor (VEGF) signaling and angiogenesis. Additionally, the mutant IDH1 consumes NADPH for $NADP^+$ production, driving a metabolic compensation through glutaminolysis, leading to the accumulation of reactive oxidation species (ROS) and oxidative damage. In the tumor microenvironment, 2-HG exerts immunosuppressive effects through upregulation of immunosuppressive macrophages and down regulation of $CD8^+$ T cells. **(B)** Safusidenib binds to the allosteric pocket in the mutant IDH1 dimer surface stabilizing the inactive form of the enzyme, thus reducing 2-HG and reversing the oncogenic effects. Created with BioRender.com.

ments include radiation-induced neurocognitive dysfunction [39], chemotherapy-associated DNA hypermutation [40], impaired fertility [41,42] and other toxicity, to preserve quality of life and alter the natural history of aLGG.

However, in contrast to the good prognosis at diagnosis, patients with recurrent WHO grade 2 glioma have poor survival [43], prioritizing the need to improve both upfront treatments to delay progression and effective salvage therapies. In addition to shortened life expectancy, patients experience a significant symptom burden including cognitive impairment, seizures, fatigue and functional impairment, with implications for quality of life and role function [44]. Thus, there is also an impact on family and caregivers, and a long-term therapeutic plan must anticipate neurological and cognitive deteriorations.

### 1.4. Mutant IDH inhibitors for glioma

Highlighting the success of precision medicines approaches, the identification of frequent mutations in the *IDH1* and *IDH2* genes in human cancers including glioma, hepatocellular carcinoma, chondrosarcoma and intrahepatic cholangiocarcinoma has provided novel therapeutic targets [13,45–47]. These trials have led to Food and Drug Administration (FDA) approvals of mutant IDH inhibitors in *IDH1* mutated cholangiocarcinoma and acute myeloid leukaemia [48] and most recently fast track designation for vorasidenib in *IDH* mutant WHO grade 2 glioma [49].

Multiple mutant IDH inhibitors have been evaluated in glioma, including ivosidenib, an IDH1-specific inhibitor and vorasidenib, a dual IDH1 and IDH2 inhibitor [8]. In a pre-surgical Phase I trial, both ivosidenib and vorasidenib were evaluated in patients with recurrent grade 2 gliomas, of whom 49% had received prior systemic treatment and 28.6% had received prior radiation therapy. Patients received a mutant IDH inhibitor (ivosidenib or vorasidenib) for 1 month prior to surgery and drug concentration and inhibition of the pathway by measuring 2-HG levels was evaluated. Both ivosidenib and vorasidenib reduced 2-HG by $>$90% compared with untreated controls, but vorasidenib showed greater brain penetrance and more consistent 2-HG suppression [7]. Notably, no pre-treatment biopsy was available prohibiting intra-patient comparison. In the INDIGO Phase III trial of patients with grade 2 *IDH* mutant gliomas, who had undergone surgery alone, vorasidenib significantly improved progression-free survival and delayed time to next intervention when compared with placebo [8].

In an earlier Phase Ib/II study, olutasidenib (FT-2102), a brain penetrant, mutant IDH1 inhibitor demonstrated preliminary clinical activity in heavily pre-treated *IDH1* mutated grade 2–4 gliomas. In this study, all 26 patients had received prior radiation therapy, 88% prior chemotherapy and 85% had grade III/IV (based on prior WHO CNS4 classification) [6]. The disease control rate (objective response plus stable disease [SD]) was 48%, two patients demonstrated partial response (PR), while eight (34%) had SD for at least 4 months.

Safusidenib (AB-218 / DS-1001b) is an oral, blood brain barrier penetrant IDH1 R132X enzyme inhibitor developed by Daiichi Sankyo. In the Phase I study, 45 patients with recurrent grade 2/3 *IDH1* mutated glioma were treated in the escalation phase (125–1400 mg BD) [9]. Treatment was well tolerated, and the maximum tolerated dose was not reached. Of 29 patients with contrast enhancing gliomas, one, three and 10 achieved complete response, PR and SD, respectively. Of the nine patients with non-enhancing gliomas, two achieved minor response and seven achieved SD. In the non-enhancing group, the median duration of treatment was 9.1 months, with 67% continuing treatment at the time of data cut-off. Additionally, 66.7% of these patients had SD and 33.3% had a minor response. DS-1001b demonstrated good brain penetration, with reduction in 2-HG, in an optional exploratory study of tumor samples obtained from six patients who developed progressive disease [9].

The outcomes for patients with grade 2/3 tumors at relapse do not appear to be influenced by either *IDH1* or 1p19q status [50,51], suggesting that the prognostic (and potentially predictive) value of this biomarker is strongest at the time of diagnosis, rather than recurrence. The INDIGO trial confirmed that IDH inhibition significantly improves progression-free survival and delays time to next intervention in patients with *IDH* mutant grade 2 gliomas within 1 to 5 years of surgery, representing early phase tumorigenesis. However, there is yet to be a study that examines mutant IDH inhibitors compared to placebo in treatment-naive patients at diagnosis. Well-designed perioperative "window of opportunity" studies can provide a unique opportunity to evaluate critical biological outcomes, identify reliable markers of drug activity and collect important multi-modal data revealing drug mechanism [52].

### 1.5. Perioperative trials

There have been few therapeutic advances in glioma due to several factors, including untested drug penetration and a failure to evaluate pharmacodynamic (PD) parameters [52]. Phase 0, perioperative and neoadjuvant studies provide a unique opportunity to study drug pharmacokinetics (PK) and penetration, PD outcomes, confirm target and off-target effects and identify predictive biomarkers. The neuro-oncology field is pivoting to this approach [52]

highlighted by prior and active perioperative studies in glioma (Supplementary Table S1) registered on clinicatrial.gov. Perioperative studies designed to include biopsy to obtain pre-treatment tissue have not previously been undertaken in patients with LGG. If feasible, they offer a rational means to examine the direct effects of a new drug. Given the precedence set by other phase 0 studies, it is highly likely that a LGG phase 0 study is feasible, ethical and will be acceptable to patients.

## 2. Objectives

We hypothesize that treatment with safusidenib following open biopsy and prior to resection in patients with *IDH1* mutated glioma, who have not received prior radiation or chemotherapy, will be feasible and determine biological activity to inform further development. The primary objective is to assess the feasibility and acceptability of undertaking a perioperative study in patients with *IDH1* mutated aLGG. We estimate that >60% of patients who are screened and undergo biopsy will complete all planned investigations and procedures.

Secondary end points include determination of toxicity of safusidenib (Table 1). The occurrence, type, severity and relationship of adverse events, laboratory abnormalities (described according to National Cancer Institute (NCI) Common Criteria for Adverse Events (CTCAE) version 5 [53]) and dose limiting toxicities (DLT) will be recorded. Safety of two stage surgery and treatment with safusidenib will be assessed with 30-day morbidity and mortality after both biopsy and resection, including delays in planned resection and need for emergency resections. The biological activity of safusidenib will be established by changes in 2-HG levels (PD biomarker) in plasma, tumor and cerebrospinal fluid (CSF) and characterising the biological effects of safusidenib on tumor samples.

To assess the PK of safusidenib when given post-biopsy and pre-resection for *IDH1* mutated LGG, PK sampling in plasma, CSF and tumor will be correlated with clinical safety and activity. Clinical anti-tumor activity will be assessed with overall response during the perioperative and adjuvant phase, defined by best response to safusidenib based on change in extent of FLAIR signal and contrast enhancement on MRI and the Response Assessment in Neuro-Oncology (RANO) criteria for aLGG [54].

To assess potential mechanisms of resistance or response to safusidenib in patients with *IDH1* mutated LGG, changes in biopsy and surgical resection tumor specimens will be correlated with clinical activity; H3K9 methylation, gene expression profiling, cancer-associated mutations and / or genetic alterations and *IDH1* mutated ctDNA in blood and CSF correlated with mutations in tumor tissues (Table 1).

### 2.1. Trial design

This is an open-label, single centre, perioperative study designed to investigate the safety, tolerability and biological activity of safusidenib in patients with *IDH1* mutated aLGG (Figure 2).

## 3. Methods

### 3.1. Participants, interventions & outcomes

Patients with a MRI diagnosis (including advanced imaging sequences) of aLGG, that require surgical resection will be screened for this study. In addition, patients with known *IDH1* mutated aLGG requiring further surgical resection who have previously only undergone surgery will also be screened. A total of 15 patients will be enrolled.

Inclusion criteria include adults ≥18 years of age with a radiological or pathological diagnosis of aLGG who do not require urgent resection for mass effect or hydrocephalus according to the treating neurosurgeon. Patients who require urgent resection, have received chemotherapy or radiation therapy or have a cerebellar or brainstem tumor are excluded from the study (Table 2).

Prior to surgery, 5–7 ml CSF will be sampled by lumbar puncture (LP) performed under general anesthesia in the lateral decubitus position. Surgical stage one will be an open biopsy. The procedure will be performed via craniotomy, with the preferred technique a craniotomy size appropriate for reopening for later definitive resection of the tumor, with initial partial resection of the tumor. This has the advantage of obtaining a large amount of tissue for analysis and will reduce operative burden on the patient if awake second stage resection is planned. The dural opening, however, will be limited to that required for the partial resection biopsy to minimize difficulties at second stage. At stage one, tissue will be sent for immediate examination by a specialist neuropathologist. If this is inconsistent with an aLGG diagnosis, the patient will be excluded from the trial and the neurosurgeon will proceed to treat the patient as appropriate, which may include resection at that operation. MRI will be performed on post-operative day one (or earlier if required) to confirm the biopsy location, exclude complications and as baseline assessment.

The histological specimens will be assessed by a specialist neuropathologist as per standard protocols. The standard immunohistochemistry panel includes glial GFAP, OLIG-2, IDH R132H, ATRX, TP53, p16 and KI-67. If the IDH1 immunohistochemistry is wild type or inconclu-

**Table 1.** Objective and outcomes of the study.

| PART A | Objectives | End points |
|---|---|---|
| Primary | 1. Assess feasibility and acceptability of Phase 0 surgical study in patients with *IDH1* mutated aLGG. | - >60% of patients who are screened and undergo biopsy complete all planned investigations and procedures |
| | 2. PK analysis of total and unbound safusidenib in tumor tissue and CSF | - PD and PK data is informative |
| Secondary | 1. Determine the toxicity of safusidenib following biopsy and prior to surgery | - Occurrence, type, severity and relationship of AE and laboratory abnormalities (described according to NCI CTCAE v 5<br>- Occurrence and type of DLTs |
| | 2. Assess safety of planned craniotomy after biopsy and treatment with safusidenib | - 30-day morbidity and mortality<br>- Delays in planned resection date<br>- Number of emergency resections |
| | 3. Establish biological activity of safusidenib in patients with *IDH1* mutated aLGG | - Changes in 2-hydroxygluterate (2-HG) levels in plasma, tumor and CSF<br>- Characterise the biological effects of safusidenib on tumor samples |
| | 4. Assess PK of safusidenib when given post-biopsy and pre-resection for *IDH1* mutated aLGG | - PK sampling in plasma, CSF and tumor correlated with clinical safety and clinical activity |
| | 5. Assess the anti-tumor activity of safusidenib in patients with *IDH1* mutated aLGG | - OR following biopsy and prior to maximal safe resection as defined by:<br>○ Best response to safusidenib based on change in extent of FLAIR signal and contrast enhancement on MRI, AND<br>○ Best response to safusidenib based on LGG-RANO |
| | 6. To identify factors that can improve the quality of the service provided to participants | - Understand patients' perspective on the peri-operative design and satisfaction with study procedures using the Research Participant Perception Survey short form. |
| Exploratory | 1. Assess potential mechanisms of resistance or response to safusidenib in patients with *IDH1* mutated aLGG following biopsy and prior to surgery | - Changes in the following will be correlated with clinical activity:<br>○ H3K9 methylation<br>○ Gene expression profiling<br>○ Differentiation genes<br>○ Cancer-associated mutations and/or genetic alterations<br>○ *IDH1* ctDNA in blood and CSF and correlate with mutations in tumor tissues |
| | 2. Develop novel imaging biomarkers of response and resistance | - Changes in diffusion ± (semi) quantitative perfusion / spectroscopic metrics correlated with clinical activity |
| | 3. Monitor changes in tumor volume in response to Safusidenib | - Objective data to make informed decisions about the efficacy of Safusidenib in patients with *IDH1* mutated LGG |
| **PART B** | **Objectives** | **End points** |
| Primary | 1. Determine the toxicity of safusidenib in patients with *IDH1* mutated aLGG following craniotomy and resection | - Occurrence, type, severity and relationship of AE and laboratory abnormalities (described according to NCI CTCAE v 5<br>- Occurrence and type of DLTs |
| Secondary | 1. Assess the anti-tumor activity of safusidenib in patients with *IDH1* mutated aLGG | - OR following maximal safe resection as defined by<br>○ Best response to safusidenib based on change in extent of FLAIR signal and contrast enhancement on MRI, AND<br>○ Best response to safusidenib based on LGG-RANO |
| | 2. To identify factors that can improve the quality of the service provided to participants | - Understand patients' perspective on the peri-operative design and satisfaction with study procedures using the Research Participant Perception Survey short form. |
| Exploratory | 1. Assess potential mechanisms of resistance to safusidenib | - Changes in the following correlated with clinical activity<br>○ H3K9 methylation<br>○ Gene expression profiling<br>○ Cancer-associated mutations and or genetic alterations<br>○ Differentiation genes<br>○ IDH1ctDNA in blood, CSF and tumor tissues |
| | 2. Assess survival | - OS<br>- PFS<br>- Time to treatment failure |
| | 3. Develop novel imaging biomarkers of response and resistance | - The changes in diffusion ± (semi) quantitative perfusion / spectroscopic metrics correlated with clinical activity |
| | 4. Monitor changes in tumor volume in response to Safusidenib | - Objective data to make informed decisions about the efficacy of Safusidenib in patients with *IDH1* mutated LGG |

sive, samples will be sent for next generation sequencing (NGS). In addition, if there are mitoses or equivocal p16 staining, the sample will be sent for NGS to confirm *CDKN2A* homozygous deletion. If the morphological diagnosis is consistent with oligodendroglioma, the sample will be sent for 1p19q testing, however these results are not required prior to safusidenib treatment. Patients with a confirmed pathological diagnosis of grade 2 aLGG with *IDH1* mutation will proceed to treatment with safusidenib.

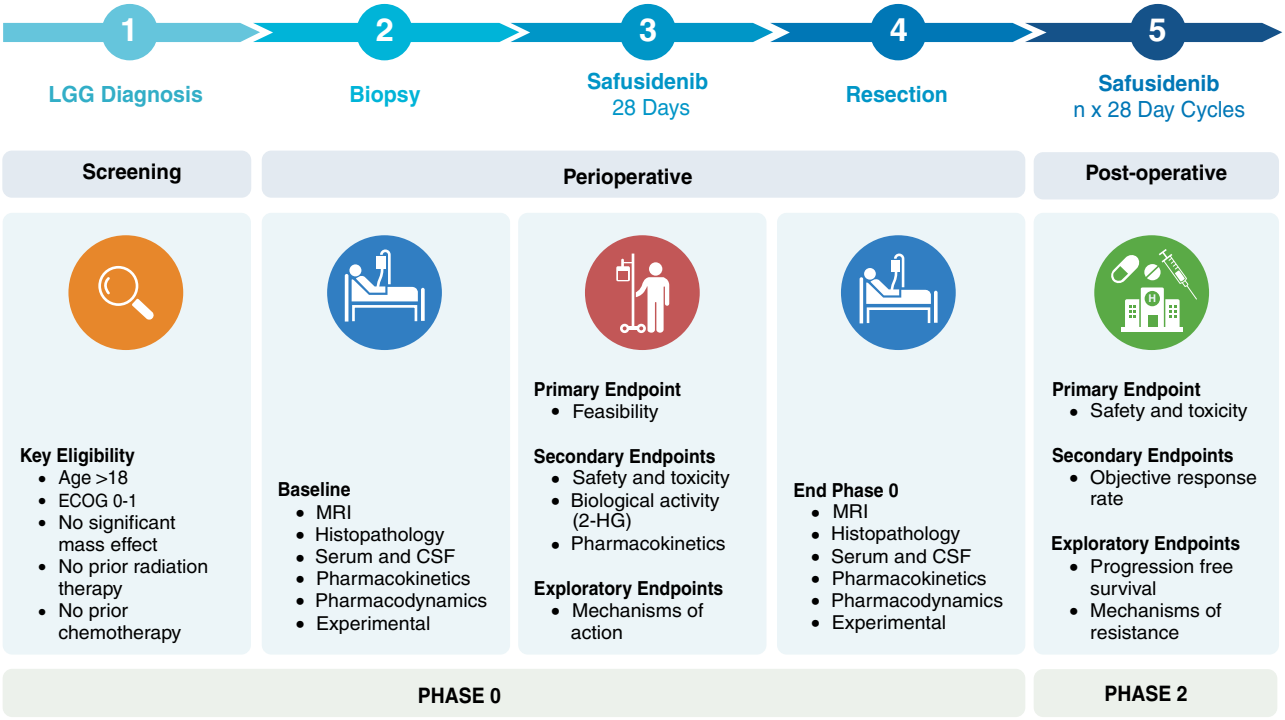


**Figure 2.** Trial Schema.
Created with BioRender.com.

Following recovery from biopsy (no <7 days and no >28 days) and confirmation of histopathology, patients will commence on oral safusidenib continuously twice daily commencing at 250 mg BD for up to 28 days (21–35 days) followed by CSF sampling via LP and planned tumor resection. Only one dose reduction and no dose escalations are permitted. Extent of resection possible and surgical adjuncts (intraoperative MRI or awake surgery with cortical mapping) will be at the discretion of the treating neurosurgeon.

While taking safusidenib, safety will be monitored by physical examination, vital signs, weight, performance status, electrocardiograms (ECG) and laboratory evaluations including glucose monitoring. All serious and non-serious adverse effects (AE) that occur from the time the patient has signed consent for the trial to 30 days after the final protocol-specified treatment are required to be reported to the Sponsor and AnHeart Therapeutics. Patients whose treatment is interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed at least once per week (if not stated otherwise) for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event. If a patient requires a study treatment interruption of greater than 28 days, they will be discontinued from study treatment.

### 3.2. Data collection, management & analysis

The tumor tissue, CSF and blood samples collected for research purposes will be labelled with a study specific code and processed according to standard operating procedures.

PK of safusidenib will be investigated to evaluate PK/PD relationships for the study population. For this purpose, blood, tumor and CSF will be collected at pre-determined points following biopsy and prior to surgery. Trough plasma samples will be collected for the whole population, for measurement of safusidenib at pre-specified time points (Table 3). Free drug concentration will not be determined in this study. It has previously been determined that safusidenib is approximately 99.6% bound to protein in human plasma at therapeutic concentrations [55]. PK CSF samples will be collected at biopsy and at surgical resection via LP. The PK parameters are not necessarily limited to safusidenib concentration ratio of biopsy to surgery for plasma. Evaluations of PK will include accumulation upon multiple dose administration, PK/PD relationship and exposure/QTc analysis. PK concentration and PK parameters (tumor/plasma ratio and tumor/CSF ratio) will be summarized by dose level using means, standard deviations, medians, minimums and maximums. Summary statistics will be computed for each sampling time and parameter as appropriate.

**Table 2.** Inclusion and exclusion criteria.

| Inclusion Criteria |
|---|
| 1. Disease as defined by: |
| a. Histologically confirmed *IDH1* mutated glioma (WHO Grade 2), OR |
| b. A new diagnosis of LGG based on MRI |
| 2. Tumors suitable for biopsy and safe for maximal resection in the opinion of the treating neurosurgeon |
| 3. Patients who in the consensus of the treating neurosurgeon require resection of the brain tumor. |
| 4. Patients who do not require immediate definitive resection of the brain tumor in the opinion of the treating neurosurgeon. |
| 5. Measurable and/or evaluable disease as per LGG-RANO criteria. |
| 6. Age $\geq$18 years of age. |
| 7. ECOG performance score 0–1. |
| 8. Life expectancy of at least 24 months, in the opinion of the investigator. |
| 9. Hematological function, as follows: |
| a. Absolute neutrophil count (ANC) $\geq 1.5 \times 109$/l |
| b. Platelet count $\geq 100 \times 109$/l |
| c. Hemoglobin $>$10 g/dl |
| d. Prothrombin time (PT) or partial thromboplastin time (PTT) $<1.5 \times$ upper limit of normal (ULN) |
| 10. Renal function, as follows: |
| a. Creatinine clearance $>$60 ml/min as per the Cockcroft-Gault equation |
| 11. Hepatic function, as follows: |
| a. Aspartate aminotransferase (AST) $<2.5 \times$ ULN (3 $\times$ ULN for participants on chronic anticonvulsive therapies known to increase transaminases). |
| b. Alanine aminotransferase (ALT) $<2.5 \times$ ULN (3 $\times$ ULN for participants on chronic anticonvulsive therapies known to increase transaminases). |
| c. Alkaline phosphatase (ALP) $<2.5 \times$ ULN (3 $\times$ ULN for participants on chronic anticonvulsive therapies known to increase transaminases). |
| d. Total bilirubin $\leq 1.5 \times$ ULN (unless Gilbert's syndrome or extrahepatic source as denoted by increased indirect bilirubin fraction). |
| 12. Reproductive criteria as follows: |
| a. For women of childbearing potential (WCBP): negative serum $\beta$ human chorionic gonadotropin ($\beta$-hCG) pregnancy test within 1 week prior to biopsy (WCBP defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally post-menopausal for at least 12 consecutive months for women $>$55 years of age) |
| 13. Willingness of male and female patients who are not surgically sterile or postmenopausal to use medically acceptable methods of birth control for the duration of the study treatment, and up to 90 days after the last dose of study drug. Sexually active men, and women using oral contraceptive pills, should also use barrier contraception. Males must agree not to donate sperm while participating in the study and for 90 days after the last dose of the study drug. |
| 14. Signed and dated IRB/independent ethics committee approved informed consent form before any screening procedures are performed. |
| 15. Ability to adhere to the study visit schedule and all protocol requirements |
| **Exclusion criteria** |
| 1. Patients who require immediate definitive resection due to degree of mass effect or symptoms |
| 2. Multicentric / multifocal tumor |
| 3. tumor of cerebellum or brainstem |
| 4. Patients who have undergone surgery for glioma within 24 months of study enrolment |
| 5. Patients who have received prior chemotherapy and / or radiation for a diagnosis of glioma |
| 6. Patients with contraindications to MRI or unwilling to undergo MRI |
| 7. History of central nervous system bleeding as defined by stroke within 6 months before enrolment |
| 8. Evidence of acute intracranial / intra-tumoral hemorrhage, except for participants with stable grade 1 hemorrhage |
| 9. Myocardial infarction within 12 months before enrolment, symptomatic congestive heart failure (New York Heart Association $\geq$class II), unstable angina, or uncontrolled hypertension |
| 10. QT prolongation or baseline QT interval corrected with Fridericia's method (QTcF) $>$450 ms (average |
| 11. Patients taking substrates of cytochrome CYP2C8, CYP2C9 and CYP3A4 with narrow therapeutic window, should be excluded unless they can be transferred to other medications prior to enrolling. Patients taking sensitive CYP 2C8, 2C9 or 3A4 substrate medications may require dosage adjustment unless they can be transferred to other medications within $\geq$5 half-lives prior to dosing |
| 12. Patients taking sensitive substrates of P-gp and BCRP transporters should be excluded unless they can be transferred to other medications prior to enrolling. Patients taking sensitive substrates of P-gp and BCRP may require dosage adjustment unless they can be transferred to other medications within $\geq$5 half-lives prior to dosing |
| 13. Patients receiving $\geq$6 mg/day of dexamethasone or equivalent |
| 14. No active infection requiring treatment with intravenous antibiotics within 14 days of biopsy |
| 15. A history of other malignancies, except adequately treated non-melanoma skin cancer, curatively treated *in situ* cancer, or other solid tumors curatively treated with no evidence of disease for $\geq$5 years |
| 16. Known positive test for human immunodeficiency virus (HIV) infection, or active hepatitis B or hepatitis C infection (Hep B or C viral load $>$100 international units / milliliter or equivalent) |
| 17. Concurrent or prior (within 7 days of enrolment) anticoagulation therapy, except low molecular weight heparins or low dose aspirin |
| 18. Enrolled in or had not yet completed at least 30 days since ending other investigational device or therapeutic study(s) |
| 19. Had major surgery within 4 weeks before enrolment or any grade 2 or higher side effects from prior surgery |
| 20. Known allergy or sensitivity to any of the excipients in Safusidenib |
| 21. Participant is pregnant or is breast-feeding |
| 22. Participant will not be available for protocol-required study visits or procedures, to the best of the participant and investigator's knowledge. |
| 23. Participant has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the participant to give written informed consent and/or to comply with all required study procedures. |
| 24. History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator would pose a risk to participant safety or interfere with the study evaluation, procedures or completion. |

**Table 3.** Pharmacokinetics of safusidenib and sample timing.

| | Day of Biopsy | D1 safusidenib | D8 safusidenib | D15 safusidenib | D28 safusidenib | Day of Surgery |
|---|---|---|---|---|---|---|
| Plasma | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| CSF | ✓ | X | X | X | X | ✓ |
| tumor | ✓ | X | X | X | X | ✓ |

Biological activity of safusidenib following biopsy and prior to surgery in patients with *IDH1* mutated LGG will be defined based on changes in 2-HG levels (PD biomarker) in plasma, tumor and CSF. We will also assess changes in 2-HG and *IDH1* ctDNA in blood and CSF using droplet digital polymerase chain reaction (PCR) after extracting cell free DNA.

To assess for potential mechanisms of response or resistance to safusidenib while overcoming the small sample size, extensive multi-omic bulk, single cell and spatial analysis will be performed. To investigate gross alterations in intra-tumoral heterogeneity in response to mutant *IDH* inhibition, we will perform whole genome sequencing (WGS), whole transcriptome sequencing (WTS) and single nuclei RNA sequencing (snRNAseq) on samples from the biopsy and resection. Additionally, we will quantify changes in metabolic activity, using bulk metabolomics (liquid chromatography-mass spectrometry and gas chromatography-mass spectrometry), and DNA methylation using Illumina EPIC array [56]. Complementing these investigations, spatial transcriptomics using *in situ* digital sequencing and spatial metabolomics will be performed on sections pre- and post-safusidenib treatment [57,58].

Descriptive statistics will be provided for selected demographics, safety, PK, PD, efficacy and biomarker data by dose and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. The small sample size of window of opportunity trials necessitates statistical considerations that differ from other clinical trials. The effect of the agent will therefore be defined based on a dichotomous biological end point: detection of drug in tumor and on-target modulation.

### 3.3. Monitoring

Toxicity will be monitored by subject incidence of all treatment-emergent AE. This will be tabulated by system organ class and preferred term. The number and percentage of subjects reporting AE will be evaluated overall and by dose level and will be tabulated by relationship to study drug. Tables of fatal AE, serious AE, those leading to withdrawal from investigational product, or other protocol-required therapies and significant treatment-emergent AE will also be provided. Occurrence and type of DLT overall and by subject will be collated and summarized by dose and group.

Clinical laboratory tests including clinical chemistry, hematology and urinalysis data will be listed and reviewed for each subject. Similarly, vital sign data and ECG over time and/or changes from baseline will be listed and reviewed. Values outside the normal laboratory reference ranges or changes, including change from baseline QTc, will be flagged as high or low on the listings and summaries may be provided.

To assess the safety of planned resection after biopsy and treatment with safusidenib, 30-day morbidity and mortality after biopsy, and after resection, will be recorded including delays in planned resection date, need for emergency resections and number of unplanned admissions.

Objective radiological response rate will be determined by the change in extent of FLAIR signal and contrast enhancement, and proportion of patients exhibiting CR or PR as per LGG-RANO criteria [59]. Progression-free survival is calculated from date of biopsy to the date of evidence of disease progression or patient death. Time to treatment failure is calculated from the date of first dose (Day 1) to cessation of drug due to progression, toxicity, death, patient refusal, or any other cause. Duration of response is defined as the time from the date of first response (CR or PR, as defined by LGG-RANO criteria) to date of first evidence of disease progression or patient death.

## 4. Conclusion

There have been few therapeutic advances in glioma due to several factors, including failure of drug penetration, the blood brain barrier and a failure to evaluate PD parameters. Perioperative studies provide a unique opportunity to study drug PK and penetration, PD outcomes, confirm target effects and to identify predictive biomarkers. Perioperative studies including biopsy to obtain pretreatment tissue have not previously been undertaken in patients with aLGG. If feasible, they offer a rational means to examine the direct effects of a new drug on critical biological outcomes. We believe that this perioperative study in aLGG is feasible, ethical and will be acceptable to patients.

Article highlights

**Introduction**

**Background & rationale**

- Adult low-grade gliomas (aLGGs) are defined by *IDH1/2* mutations which lead to accumulation of 2-HG, an oncometabolite affecting tumorigenesis.
- 2-HG inhibits $\alpha$-KG-dependent enzymes, affecting epigenetic regulation, collagen synthesis and cell signaling, hindering progenitor cell differentiation and promoting cancer. In addition, 2-HG promotes angiogenesis, an immunosuppressive tumor microenvironment and oxidative damage.
- aLGGs grow slowly, diffusely infiltrating the brain and are difficult to cure.
- Emergence of targeted mutant IDH inhibitors has shifted focus toward identifying prognostic markers and future combination studies.

**Current treatment of aLGG**

- Treatment includes maximal safe surgical resection, radiation therapy and sequential chemotherapy.
- Early, extensive surgery improves overall survival.
- Active surveillance with MRI is suitable for some patients to delay side effects.

**Mutant IDH inhibitors for glioma**

- Multiple mutant IDH inhibitors have shown promise in glioma.
- Vorasidenib (IDH1/2 inhibitor) improved progression-free survival in the INDIGO Phase III trial.
- Safusidenib (DS-1001b, AB-218) is an orally available small molecule inhibitor of mutant IDH1 with demonstrated brain penetration and clinical activity in Phase I trials.

**Perioperative trials**

- There have been few therapeutic advances in glioma due to challenges in measuring drug penetration and pharmacodynamic (PD) evaluation.
- Perioperative trials, including biopsy to obtain pre-treatment tissue, are feasible and offer a means to examine the direct effects of new drugs.
- These studies allow evaluation of drug pharmacokinetics (PK) and PD outcomes.

**Objectives**

- Hypothesis: Treatment with safusidenib following biopsy and prior to resection in newly diagnosed *IDH1* mutated glioma is feasible.
- Estimate: $>60\%$ of screened patients completing planned investigations and procedures.
- Primary objective: Assess feasibility and acceptability of a perioperative study in *IDH1* mutated aLGG patients.
- Secondary end points: Determine safusidenib toxicity, safety of two-stage surgery and biological activity by changes in 2-HG levels.

**Methods**

**Participants, interventions, & outcomes**

- Key inclusion: Adults $\geq 18$ years with aLGG diagnosis not requiring urgent resection.
- Key exclusion: prior chemotherapy/radiation, cerebellar/brainstem tumors.
- Procedures: Open biopsy, oral safusidenib, second-stage resection, continued safusidenib post-resection.
- Data collection: tumor tissue, CSF and blood samples processed per protocols.
- PK/PD relationships: Evaluated by blood, tumor and CSF samples.
- Biological activity: Assessed by changes in 2-HG levels and *IDH1* ctDNA.

**Data collection, management, & analysis**

- Tumor tissue, CSF and blood samples collected for research.
- Safusidenib PK will be investigated to evaluate PK/PD relationships.
- Translational end points include paired whole-genome transcriptome profiling, single nuclei RNA sequencing, bulk metabolomics and DNA methylation.
- Spatial transcriptomics using *in situ* digital sequencing and spatial metabolomics on sections pre- and post-safusidenib treatment.
- Descriptive statistics for demographics, safety, PK, PD, efficacy and biomarker data by dose and time.

**Monitoring**

- Toxicity: Monitored by adverse events, clinical tests and vital signs.
- Safety of surgery: 30-day morbidity and mortality recorded post-biopsy and resection.
- Radiological response: Determined by MRI changes and LGG-RANO criteria.
- Progression-free survival and time to treatment failure: Calculated from biopsy date.

**Conclusion**

- Perioperative studies in aLGG offer a unique opportunity to study drug effects and are feasible, ethical and acceptable to patients.

## Author contributions

Conceptualization, JR Whittle, M Rosenthal and KJ Drummond; methodology, JR Whittle, KJ Drummond, M Rosenthal, S Freytag and SA Best; writing – original draft preparation: SA Cain, M Topp and JR Whittle; writing – review and editing: all; writing – revision: SA Cain, S Freytag, SA Best, JR Whittle and KJ Drummond; funding acquisition, M Rosenthal, JR Whittle and KJ Drummond; supervision, JR Whittle and KJ Drummond. All authors have read and agreed to this version of the manuscript.

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## Writing disclosure

No writing assistance was utilized in the production of this manuscript.

## Ethical conduct of research

The protocol has been approved by The Royal Melbourne Hospital Human Research Ethics Committee (HREC Reference Number: HREC/83588/MH-2022). The study will be performed in accordance with the ethical principles of the Declaration of Helsinki and conducted in adherence to the study protocol, applicable Good Clinical Practices, and applicable laws and country-specific regulations in which the study is being conducted. Informed consent will be obtained from all patients before any study-related procedures are conducted.

## ORCID

Sarah A Cain https://orcid.org/0000-0002-6610-4617

Robert Tobler https://orcid.org/0009-0002-6983-556X
Saskia Freytag https://orcid.org/0000-0002-2185-7068
Sarah A Best https://orcid.org/0000-0002-4232-9432
James R Whittle https://orcid.org/0000-0002-4740-2037
Katharine J Drummond
https://orcid.org/0000-0002-8152-2120

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