Study Title

**LUMOS:** Low & Intermediate Grade Glioma **Umbrella Study of Molecular Guided Therapies** – Pilot Study

**NHMRC CTC protocol number**

COGNO 19/05, CTC 0267

**Protocol version number and date**

Protocol version 1.2 dated 13 November 2019

**Australian Sponsor:**

The University of Sydney

NSW 2006 Australia

This study is a collaboration between the Cooperative Trials Group for Neuro-Oncology (COGNO) and the NHMRC Clinical Trials Centre, University of Sydney.

**Study Chair:**

Associate Professor Hui Gan

**Coordinating Centre:**

NHMRC Clinical Trials Centre

92-94 Parramatta Road

Camperdown NSW 2050

Telephone: 61-2-9562-5000

Fax: 61-2-9565-1863

Email: lumos@ctc.usyd.edu.au

CONFIDENTIAL
Senior statistician: Elizabeth Barnes, NHMRC Clinical Trials Centre

CTC Clinical Lead: Mustafa Khasraw, NHMRC Clinical Trials Centre

Project Manager: Merryn Hall, NHMRC Clinical Trials Centre

Protocol Development Working Party
The following individuals also contributed to the design and development of this protocol:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Organisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anna Nowak</td>
<td>Medical Oncologist</td>
<td>University of Western Australia, WA</td>
</tr>
<tr>
<td>Ben Kong</td>
<td>Clinical Research Fellow</td>
<td>NHMRC CTC, University of Sydney</td>
</tr>
<tr>
<td>Sonia Yip</td>
<td>Translational Research Lead, Senior Research Fellow</td>
<td>NHMRC CTC, University of Sydney</td>
</tr>
<tr>
<td>Candace Carter</td>
<td>Research Development Lead</td>
<td>NHMRC CTC, University of Sydney</td>
</tr>
</tbody>
</table>
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
</tr>
<tr>
<td>AYA</td>
<td>Adolescent and young adult</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>CR</td>
<td>Complete Response</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography (scan)</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>CTC</td>
<td>NHMRC Clinical Trials Centre, University of Sydney</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>EGFR</td>
<td>Epidermal Growth Factor receptor</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FFPE</td>
<td>Formalin-fixed paraffin-embedded</td>
</tr>
<tr>
<td>GBM</td>
<td>Glioblastoma or glioblastoma multiforme</td>
</tr>
<tr>
<td>HREC</td>
<td>Human Research Ethics Committee</td>
</tr>
<tr>
<td>IC_{50}</td>
<td>50% maximal inhibitory concentration</td>
</tr>
<tr>
<td>ICMJE</td>
<td>International Committee of Medical Journal Editors</td>
</tr>
<tr>
<td>IDH</td>
<td>Isocitrate Dehydrogenase</td>
</tr>
<tr>
<td>IDSMDC</td>
<td>Independent Data, Safety Monitoring Committee</td>
</tr>
<tr>
<td>MBS</td>
<td>Medicare Benefits Scheme (Australia)</td>
</tr>
<tr>
<td>MTB</td>
<td>Molecular Tumour Board</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PBS</td>
<td>Pharmaceutical Benefits Scheme (Australia)</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>Platelet-derived growth factor receptor alpha</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression Free Survival</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive Disease</td>
</tr>
<tr>
<td>PR</td>
<td>Partial Response</td>
</tr>
<tr>
<td>SD</td>
<td>Stable Disease</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
</tr>
</tbody>
</table>
Table of Contents

SYNOPSIS AND SCHEMA ............................................................................................................. 6
1. BACKGROUND ....................................................................................................................... 10
   1.1 Background and Study Rationale .................................................................................. 10
   1.2 Rationale for Umbrella Design .................................................................................. 12
   1.3 Feasibility and Role of Re-resection at Progression for Grade 2/3 Gliomas .............. 12
   1.4 Potential Drug Targets for Patients Enrolled in LUMOS .......................................... 13
   1.5 Rationale for Pilot study .............................................................................................. 14
2. AIM AND OBJECTIVES ....................................................................................................... 14
3. DESIGN .................................................................................................................................. 15
4. STUDY POPULATION .......................................................................................................... 16
   4.1 Target Population ........................................................................................................... 16
       4.1.1 Inclusion Criteria ................................................................................................. 16
       4.1.2 Exclusion Criteria ............................................................................................... 16
   4.2 Study Enrolment .......................................................................................................... 17
       4.2.1 Screening ............................................................................................................. 17
       4.2.2 Registration ........................................................................................................ 17
       4.2.3 Specimen Transport to Central Laboratory for Molecular Testing ..................... 17
5. STUDY PLAN ......................................................................................................................... 17
   5.1 Molecular Phenotyping ................................................................................................. 17
   5.2 Molecular Tumour Board (MTB) ................................................................................ 17
   5.3 Identification of Treating Physicians .......................................................................... 17
   5.4 Informing patients of screening results ..................................................................... 18
   5.5 Discloser of clinically significant information ...................................................... 18
   5.6 Treatment Following Delivery of Molecular Tumour Board Report ....................... 18
       5.6.1 Follow Up Assessments .................................................................................... 18
       5.4.2 Concomitant Medications ............................................................................... 19
       5.4.3 Concomitant Medication Reporting ................................................................. 19
   5.7 Study Follow Up Discontinuation ............................................................................. 19
6. ASSESSMENT PLAN ............................................................................................................. 20
   6.1 Table 4: Schedule of Assessments ........................................................................... 20
   6.2 Details of Assessments............................................................................................... 22
       6.2.1 Clinical Assessment ............................................................................................ 22
       6.2.2 Imaging ............................................................................................................... 22
       6.2.3 Blood Collection ............................................................................................... 22
       6.2.4 Tissue Collection .............................................................................................. 22
   6.3 Follow-up After Treatment ......................................................................................... 22
7. OUTCOMES, ENDPOINTS AND OTHER MEASUREMENTS ........................................ 22
   7.1 Primary Endpoints ....................................................................................................... 23
       7.1.1 Number of patients enrolled ............................................................................. 23
       7.1.2 Number of patient that successfully completed molecular profiling ............. 23
   7.2 Secondary Endpoints ................................................................................................. 23
       7.2.1 Proportion of screened patients enrolled ......................................................... 23
       7.2.2 Proportion of patients that successfully complete molecular profiling .......... 23
       7.2.3 Turn-around time (TAT) of molecular screening ............................................. 23
       7.2.4 Matching of MTB recommendations with pharmaceutical agents ............... 23
       7.2.5 Proportion of patients in whom a MTB recommended agent is obtained & used 23
       7.2.6 Response to any MTB or clinician-recommended pharmaceutical agent .... 23
       7.2.7 Number of patients who undergo further surgical debulking at progression ... 23
       7.2.8 The number of patients who were screened for the study ................................ 23
   7.3 Tertiary/correlative measures ....................................................................................... 24
       7.3.1 The associations between clinical endpoints and potential biomarkers .......... 24

LUMOS protocol, COGNO 19/05, CTC0267
Version 1.2 dated 13 November 2019  Page 4 of 33
Confidential
8. CENTRAL REVIEW ............................................................................................................... 24
  8.1 Screening for eligibility .................................................................................................. 24
9. CENTRAL STORAGE OF BIOSPECIMENS ...................................................................... 24
  9.1 Central tissue collection ............................................................................................... 24
  9.2 Central blood collection ............................................................................................... 24
10. STATISTICAL CONSIDERATIONS ................................................................................... 25
   10.1 Sample Size ................................................................................................................ 25
   10.2 Statistical Analysis ..................................................................................................... 25
   10.3 Interim analyses ......................................................................................................... 25
11. STUDY ORGANISATION and COMMITTEES .................................................................. 25
   11.1 Study coordination ..................................................................................................... 25
   11.2 Trial Management Committee .................................................................................. 26
   11.3 Molecular Tumour Board Committee ...................................................................... 26
12. ADMINISTRATIVE ASPECTS ......................................................................................... 26
   12.1 Ethics and regulatory compliance .............................................................................. 26
   12.2 Confidentiality .......................................................................................................... 26
   12.3 Protocol amendments ............................................................................................... 26
   12.4 Data Handling and Record Keeping ........................................................................... 26
   12.5 Study Monitoring ....................................................................................................... 27
   12.6 Audit and Inspection ................................................................................................. 27
   12.7 Clinical Study Report ................................................................................................ 27
   12.8 Publication Policy ...................................................................................................... 27
13. PROTOCOL AMENDMENTS ............................................................................................ 27
14. REFERENCES ...................................................................................................................... 28
15. APPENDICES .................................................................................................................... 30
   15.1 Appendix 1: ECOG Performance Status34 ................................................................ 30
   15.2 Appendix 2: Recommended MRI Protocol ................................................................. 31
SYNOPSIS AND SCHEMA

Background

Grade 2 and 3 gliomas (G2/3 gliomas) are the second largest group of malignant brain tumours in adults. The Australian Institute of Health and Welfare (AIHW) projects that 1,935 Australians will be diagnosed with primary brain tumours in 2018, of whom approximately 17% will have G2/3 gliomas (~329 patients). Although the outcomes for G2/3 gliomas at progression/recurrence closely approach the poor outcomes for glioblastoma (GBM), there are virtually no trials for patients with relapsed G2/3 gliomas. This study will provide trial options for Australian patients with G2/3 gliomas.

LUMOS is a national Australian umbrella study specifically for patients with G2/3 gliomas to match patients with targeted therapies based on molecular testing using contemporaneous tumour tissue. It maximises efficacy by matching mutations to drugs, whilst using an efficient Simon 2-stage design suited for small patient numbers. It also includes a chemotherapy comparator arm that will be used to assist in the assessment of efficacy data.

The current study is a 12-month pilot to assess the feasibility of the main LUMOS study by setting up 5 pilot sites across the country as a proof of concept.

Aim

To perform a pilot study at:
- Five Australian pilot sites and
- Demonstrate the feasibility of establishing and recruiting to the LUMOS protocol at these five sites

This pilot study will generate preliminary feasibility and proof of concept data to support the full study.

Primary endpoints

1) **Number of patients enrolled.**
This is defined as the absolute number of patients successfully enrolled for molecular phenotyping over the lifetime of the study.

2) **Number of patients that successfully complete molecular profiling.**
This is the absolute number of patients for whom molecular profiling was successfully completed over the lifetime of the study.

Secondary endpoints

3) **Proportion of screened patients enrolled**
This is defined as the proportion of patients enrolled compared to those who were screened.

4) **Proportion of patients that successfully complete molecular profiling**
This is defined as the proportion of patients for whom molecular profiling was successfully completed, as a proportion of those who were enrolled.

5) **Turn-around time (TAT) of molecular screening.**
This is defined as the time taken from patient consent to central receipt of a completed Molecular Tumour Board Report. In addition, the time from receipt of tumour tissue to a completed Molecular Tumour Board report...
Tertiary and correlative endpoints

11) The associations between clinical endpoints and potential predictive/prognostic biomarkers (tissue and circulating)

Bloods and tissues, as outlined in Table 4, will be collected and stored for future investigation of resistance and biomarkers.

These translational research studies may include but not be limited to:

- Immune cell infiltration analyses by immunohistochemistry
- Gene expression studies
- Analysis of circulating biomarkers of inflammation
- Studies that may help to understand the course of this cancer and related diseases;

Biomarkers may be RNA-based (single entity or entire expressed genome, RNA, miRNA), DNA-based (single entity or whole genome, germ line or tumour related), protein-based or other entities.

Tissue biomarkers may also be investigated as prognostic and/or predictive biomarkers of clinical endpoints.

Since the identification of new biomarkers correlating with disease activity and the efficacy or safety of treatment are rapidly evolving, the definitive list of biomarkers remains to be determined.

Design

This is a multi-centre, pilot study enrolling a cohort of patients with contemporaneous tissue at the time of progression after prior radiotherapy and chemotherapy, to determine the feasibility of undertaking molecular phenotyping with a molecular panel to aid
subsequent treatment selection.

**Population**
Adults with histologically or cytologically confirmed grade 2/3 gliomas, progressing after radiotherapy and chemotherapy, who are able to provide recent tumour tissue (within 6 months of study entry) for molecular phenotyping.

**Study intervention**
Molecular profiling using the Illumina TruSight 170 panel.

**Assessments**
Patients will undergo molecular testing using a standardised molecular panel, with subsequent generation of a Molecular Tumour Board Report. This will be provided to the investigators as well as the Treating Physician.

In the post-study follow up period, subsequent treatments will be at the discretion of the Treating Physician. Treatments provided to the patient and their efficacy will be monitored. Although MRI scans every 2 months are encouraged, these assessments will be performed at the discretion of the Treating Physician.

At the time of progression, if the patient undergoes surgery (at the discretion of the Treating Physician), further molecular testing will be performed if appropriate.

Translational research bloods at screening (or pre-surgery), delivery of molecular tumour board report, progressive disease and end of follow up.

**Statistical considerations**
This is pilot study with a pragmatic sample size of 10 patients across 5 sites in 12 months.
Study Schema

Duration of recruitment: up to 12 months

Duration of follow-up: up to 24 months from registration

Recurrent grade 2/3 glioma

Registration

Tissue obtained within the last 6 months that is available for molecular profiling

Molecular profiling

Actionable mutation identified: if an actionable mutation is identified, information about corresponding targeted treatments via an existing clinical trial or pharmaceutical access program will be provided to the treating clinician

No actionable mutation identified: if no actionable mutation is identified or in cases where access to an appropriate targeted agent is not available, standard of care treatments will be offered to participants by the treating clinician

Follow up: treatment (decided at the discretion of the treating physician) recorded

Progression: at the time of progression, patients may be offered the option of further re-resection (if applicable) and repeat molecular profiling. A new Molecular Tumour Board report would be generated.
1. BACKGROUND

1.1 Background and Study Rationale

Brain tumours are rare cancers, being only the 15\textsuperscript{th} most common cancers by incidence in Australia in 2017.\(^1\) Although rare, they are devastating to the patient and their families. They are the 5\textsuperscript{th} most lethal cancer in the general population.\(^1\) However, they are actually the most lethal solid tumour for paediatric and adolescents and young adult (AYA) patients (aged 0-24 years of age).\(^1\) There has been minimal improvement in survival for brain cancers since 1984.\(^1\)

Understandably, most research to date has focused on grade 4 glioma (also known as glioblastoma or GBM), which is the most common type of primary malignant brain tumour (~45\% of primary brain tumours) and has the shortest overall survival (median survival 15 months).\(^1,3\)

Grade 2 and 3 (G2/3) gliomas are comprised of low-grade gliomas (grade 2 gliomas) and intermediate grade gliomas (grade 3 gliomas), with the difference in grading based on WHO morphological criteria. They comprise about 17\% of malignant brain tumours, or about 329 of the projected 1935 brain tumour patients in 2018.\(^1,2\) They make up the most common group of adult brain tumours after GBM.\(^2\) In addition to morphological grading, these tumours also have different molecular phenotypes and prognoses at diagnosis (Table 1). Most are characterised by mutations in Isocitrate Dehydrogenase (\textit{IDH}) 1 or 2. A subset of \textit{IDH}-mutated G2/3 gliomas are called oligodendroglioma, which are characterised by the presence of a second and characteristic chromosomal deletion of the short arm of chromosome 1 and long arm of chromosome 19 (1p/19q codeletion). The standard of care for patients with G2/3 gliomas has evolved in the last 5 years, with studies showing substantial and significant improvements in survival if radiotherapy and chemotherapy are given at initial diagnosis in high risk grade 2 gliomas\(^4\) and in most patients with grade 3 gliomas.\(^5,6\) Overall, with the exception of \textit{IDH} wildtype Grade 3 gliomas (which behave like GBM), the survival of G2/3 gliomas at diagnosis is much better than that of GBM.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Molecular characteristics</th>
<th>First line treatment following maximal safe resection</th>
<th>Median overall survival from diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 glioma (GBM)</td>
<td>\textit{IDH} wild type</td>
<td>Chemoradiotherapy with temozolomide</td>
<td>~ 15 months(^7)</td>
</tr>
<tr>
<td>Grade 3 astrocytoma</td>
<td>\textit{IDH} wildtype</td>
<td>Chemoradiotherapy with temozolomide</td>
<td>~ 20 months(^8)</td>
</tr>
<tr>
<td>Grade 3 astrocytoma</td>
<td>\textit{IDH mutated} 1p19q non-co-deleted</td>
<td>Radiotherapy with temozolomide</td>
<td>~ 5 years(^8)</td>
</tr>
<tr>
<td>Grade 3 oligodendroglioma</td>
<td>\textit{IDH mutated} 1p19q co-deleted</td>
<td>Radiotherapy with PCV chemotherapy</td>
<td>&gt; 11 years(^8)</td>
</tr>
<tr>
<td>Grade 2 astrocytoma</td>
<td>\textit{IDH wildtype}</td>
<td>Consider radiotherapy and chemotherapy</td>
<td>~ 5 years(^8)</td>
</tr>
<tr>
<td>Grade 2 astrocytoma (high risk)</td>
<td>\textit{IDH mutated} 1p19q non-co-deleted</td>
<td>Radiotherapy with PCV chemotherapy</td>
<td>~ 8 years(^8)</td>
</tr>
<tr>
<td>Grade 2 oligodendroglioma (high risk)</td>
<td>\textit{IDH mutated} 1p19q co-deleted</td>
<td>Radiotherapy with PCV chemotherapy</td>
<td>&gt;12 years(^8)</td>
</tr>
</tbody>
</table>

In contrast to the good survival of G2/3 gliomas at diagnosis (Table 1), their survival at inevitable relapse is actually very poor regardless of grade (Table 2). Median progression free survival (mPFS) is approximately 9 months (range 2-11) and median overall survival (mOS) is approximately 15 months (range 2-20). Also, most are now relapsing post radiotherapy and chemotherapy, limiting their therapeutic options further. Importantly in the relapsed setting, the very limited literature does not support differential outcomes in oligodendrogliomas (whether defined
histologically or by 1p/19q molecular typing) compared to non-oligodendrogial tumours.\textsuperscript{9,10} Similarly, outcomes at recurrence do not appear to be influenced by IDH status. Therefore, it appears that the prognostic value of IDH mutation in G2/3 glioma is strongest from the time of diagnosis to the time of recurrence, rather than at the time of recurrence.\textsuperscript{10} These limited data needs to be interpreted with caution and more research is required. Furthermore, these patients also experience a high symptom burden throughout their disease trajectory, including seizures, cognitive impairment, and functional impairment, depending on the site of the tumour.

Table 2: Summary of Treatment for G2/3 Gliomas at Recurrence

<table>
<thead>
<tr>
<th>Post-radiotherapy but no prior systemic therapy</th>
<th>Pre-treated with Radiotherapy and systemic therapy</th>
<th></th>
<th>All 3 groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>G2 gliomas</td>
<td>G3 gliomas</td>
<td>Mixed G2 and G3</td>
<td>Median(range)</td>
</tr>
<tr>
<td>Chemo\textsuperscript{10-13}</td>
<td>RR: 27%\textsuperscript{13}</td>
<td>RR: 44-63%\textsuperscript{11,12}</td>
<td>RR: 54%\textsuperscript{10}</td>
</tr>
<tr>
<td>mPFS: 10mo\textsuperscript{13}</td>
<td>mPFS: 7-10mo\textsuperscript{11,12}</td>
<td>mPFS: 8mo\textsuperscript{10}</td>
<td>mPFS: 9mo (7-10)</td>
</tr>
<tr>
<td>PFS6: 67%\textsuperscript{10}</td>
<td>PFS6: N/A</td>
<td>PFS6: 67%\textsuperscript{10}</td>
<td>mOS: 15mo (14-20)</td>
</tr>
<tr>
<td>PFS12: N/A</td>
<td>PFS12: N/A</td>
<td>PFS12: 25%\textsuperscript{10}</td>
<td></td>
</tr>
<tr>
<td>mOS: 14mo\textsuperscript{13}</td>
<td>mOS: 16-20mo\textsuperscript{11,12}</td>
<td>mOS: 14mo\textsuperscript{10}</td>
<td></td>
</tr>
<tr>
<td>OS12: N/A</td>
<td>OS12: N/A</td>
<td>OS12: 60%\textsuperscript{10}</td>
<td></td>
</tr>
<tr>
<td>OS24: N/A</td>
<td>OS24: N/A</td>
<td>OS24: 23%\textsuperscript{10}</td>
<td></td>
</tr>
<tr>
<td>Pre-treated with Radiotherapy and systemic therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo\textsuperscript{14-16}</td>
<td>RR: 47%\textsuperscript{17*}</td>
<td>RR: 13-23%\textsuperscript{14-16}</td>
<td>N/A</td>
</tr>
<tr>
<td>mPFS: 10mo\textsuperscript{17*}</td>
<td>mPFS: 4-8mo\textsuperscript{14-16}</td>
<td>mPFS: 6mo (4-10)</td>
<td></td>
</tr>
<tr>
<td>PFS6: 76%\textsuperscript{17}</td>
<td>PFS6: 30-40%\textsuperscript{14,15}</td>
<td>PFS6: 40 (30-76)</td>
<td></td>
</tr>
<tr>
<td>PFS12: 39%\textsuperscript{17*}</td>
<td>PFS12: 5-8%\textsuperscript{14,15}</td>
<td>mOS: 8 mo (7-19)</td>
<td></td>
</tr>
<tr>
<td>mOS: N/A</td>
<td>mOS: 7-19mo\textsuperscript{14,15}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS6: N/A</td>
<td>OS12: 23%\textsuperscript{16}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted ± Chemo\textsuperscript{9,17-20}</td>
<td>RR: 0%\textsuperscript{9}</td>
<td>RR: 0-8%\textsuperscript{9,18}</td>
<td>N/A</td>
</tr>
<tr>
<td>mPFS: 11mo\textsuperscript{9}</td>
<td>mPFS: 0 \textsuperscript{19,20}</td>
<td>mPFS: 50% (15-24)</td>
<td></td>
</tr>
<tr>
<td>PFS6: N/A</td>
<td>mPFS: 2-3mo\textsuperscript{19,20}</td>
<td>mOS: 7mo (7-19)</td>
<td></td>
</tr>
<tr>
<td>PFS12: 39%\textsuperscript{9}</td>
<td>PFS12: 14%\textsuperscript{19}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mOS: N/A</td>
<td>mOS: 2-8mo\textsuperscript{19,20}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS6: 94%\textsuperscript{9}</td>
<td>OS6: N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab\textsuperscript{21,22}</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments:</td>
<td>Chemo: TMZ,\textsuperscript{10,13,17} hydroxyurea\textsuperscript{9}</td>
<td>Chemo: TMZ,\textsuperscript{11} PCV,\textsuperscript{12} cyclophosphamide,\textsuperscript{14} irinotecan,\textsuperscript{15} paclitaxel,\textsuperscript{16} hydroxyurea\textsuperscript{19}</td>
<td>Chemo: lomustine\textsuperscript{18}, hydroxyurea\textsuperscript{8}</td>
</tr>
<tr>
<td></td>
<td>Targeted: erlotinib,\textsuperscript{20} imatinib\textsuperscript{9}</td>
<td>Targeted: sunitinib\textsuperscript{18}, imatinib\textsuperscript{9}</td>
<td>Targeted: imatinib\textsuperscript{19}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>** These studies contained approximately two thirds patients without prior systemic therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

mOS: median overall survival; mPFS: median progression free survival; N/A: Not available; OS6: 6-month survival; OS12: 12-month survival; OS24: 24-month survival; PFS6: 6 months PFS; PFS12: 12-month PFS; RR: Response rate

At the time of progression, patients with relapsed G2/3 gliomas have limited and generally ineffective standard of care (SOC) treatments like chemotherapy (Table 2). There is also little consensus in Australia about how these patients should be managed.\textsuperscript{23} Worse still, trials for this
G2/3 glioma population with recurrent disease are very limited, as pharmaceutical companies feel that this less common disease scenario is not profitable for drug development. Whilst initial trials in G2/3 gliomas are rarely supported by the pharmaceutical industry, once proof of concept and a signal for response is demonstrated, it is more likely that they will support a definitive registration trial, deeming it lower risk and with more realistic potential for commercial return at that time. However, the ‘valley of death’ for drug development in this population needs to be crossed through academic trials.24

1.2 Rationale for Umbrella Design

LUMOS is an umbrella trial designed to rationally test targeted agents for patients with relapsed G2/3 glioma. An umbrella study takes patients with one disease group and then allocates them to different treatments based on some biological rationale. This approach is particularly relevant for the use of targeted agents, in which the presence of the target is required for efficacy. By enrolling patients suitable for therapeutic debulking, the availability of contemporaneous tissue for molecular phenotyping will overcome one of the major problems with prior trials studying targeted agents in G2/3 gliomas, in which the lack of patient selection and/or use of archival tissue has made it impossible to tell whether failure was due to intrinsic resistance or just the unfortunate inclusion of patients lacking the target. Patients who have undergone surgery within 6 months prior to enrolment and who have not received any subsequent cancer therapy may also be screened for study enrolment. To put this in context, many of the most successful drugs today would have failed had they been trialled in populations lacking the target. An example is the development of trastuzumab for HER2 positive breast cancer. Similarly, Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitors in unselected lung cancer populations were ineffective but have since become pivotal treatment when offered only to lung cancer patients with relevant activating mutations in the EGFR kinase domain. Given the poor survival of patients with recurrent G2/3 glioma post radiotherapy and the chemotherapy, and the better tolerability of targeted agents in general over standard of care treatments like chemotherapy, the ability to typed patients tumours for potential treatment with a targeted agents will be attractive to many clinicians and patients.

The LUMOS umbrella design is also innovative because of the logical inclusion of a contemporaneous comparator arm for patients who receive standard of care chemotherapy due to the lack of actionable mutations or for patients that have actionable mutations but no access to a suitable drug. This is particularly relevant as our comprehensive review of the literature shows minimal historical data about outcomes in molecularly defined subgroups against which to benchmark efficacy data. The availability of a comparator group reduces the problem of selection bias inherent in single arm Phase 2 studies. In this way, we maximise the chances of efficiently rejecting inactive drugs whilst moving forward with active drugs. At the same time, it avoids the ethical problem of denying patients with a likely actionable mutation access to a relevant drug as may happen in a randomised study, in which some such patients could be randomised to a standard of care arm.

1.3 Feasibility and Role of Re-resection at Progression for Grade 2/3 Gliomas

Repeat craniotomy and resection at the time of disease recurrence is considered feasible in most patients and can provide significant benefits.25 One study estimated that up to 86% of patients could safely undergo re-resection at the time of progression.26 Of these, up to 50% will achieve a gross total resection.27 In another study, tumour debulking combined with adjuvant treatment after surgery resulted in a significant improvement in PFS compared to those who underwent surgery only (24 vs 10 months, p=0.005), although these data pre-dated the routine use of postoperative adjuvant therapy at initial diagnosis.26
A major advantage of re-resection is the information provided about changes in tumour biology at the time of progression. At re-operation, transformation to a higher grade had occurred in 24% of patients. Radiological enhancement alone is not sufficient to predict malignant progression. In one study, 23% of patients with only increase in T2/FLAIR abnormality showed increased tumour grade (23%) whilst 18% of those with contrast enhancement showed no increase in tumour grade. Equally importantly for this study, surgery allows confirmation of molecular phenotype at relapse. For example, a case report of acquisition of the highly actionable BRAF V600E mutation at progression has been described.

1.4 Potential Drug Targets for Patients Enrolled in LUMOS

Currently, only IDH mutation and 1p/19q codeletion testing are routinely available in most centres, with variable access to ATRX mutations and p53 testing. The importance of identifying actionable mutations is that many of these can be matched with specific drugs. Whilst individually of modest prevalence, collectively there are potentially a large number of actionable mutations for these patients. Patients with IDH mutations (89-100% of cases), likely already known from standard of care testing in many sites, may benefit from additional profiling where a false positive from immunohistochemistry is suspected (~10% of younger patients), due to lack of access to an IDH inhibitor or for treatment after progression on an IDH inhibitor. For every 10 such patients who undergo molecular testing, up to 9 patients will have actionable mutations other than an IDH mutation.

Table 3: Potential Drug Therapies by Mutations Status in Overall LUMOS Study

<table>
<thead>
<tr>
<th>Gene Mutation</th>
<th>IDH mutated, 1p/19q co-deleted</th>
<th>IDH mutated, 1p/19q intact</th>
<th>IDH wild type</th>
<th>Potential Targeted Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IDH</strong> mutation</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
<td>Multiple including IDH inhibitors, IDH vaccines, PARP inhibitors, immunotherapy</td>
</tr>
<tr>
<td><strong>PIK3CA</strong> mutation</td>
<td>4-20%²⁹,³⁰ 5%³⁰</td>
<td>2-9%²⁹,³⁰</td>
<td>PI3K inhibitors</td>
<td></td>
</tr>
<tr>
<td><strong>PIK3R1</strong> mutation</td>
<td>9%²⁹</td>
<td>Occasional²⁹</td>
<td>Rare²⁹</td>
<td>PI3K inhibitors</td>
</tr>
<tr>
<td><strong>BRAF V600E</strong> mutation</td>
<td>1-5%³¹ 0%³¹ 0%²⁹</td>
<td>BRAF inhibitors, MEK inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BRAF</strong> amplification</td>
<td>39%³² 2%³² 17%³²</td>
<td>RAF inhibitors, MEK inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PDGFRA</strong> amplification</td>
<td>~1%²⁹ 0-16%²⁹ 0-28%²⁹</td>
<td>Multi-kinase inhibitors that include PDGFR</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CDK4</strong> amplification</td>
<td>Rare²⁹ Rare²⁹ 7%²⁹</td>
<td>CDK4/6 inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EGFR</strong> amplification or mutation</td>
<td>6%³⁰ 15%³⁰ 27-89%²⁹,³⁰</td>
<td>EGFR inhibitors or EGFR ADCs</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PTEN</strong> inactivating mutation</td>
<td>2%³⁰ 0%³⁰ 20-23%²⁹,³⁰</td>
<td>PI3K inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MDM4</strong> amplification</td>
<td>0%²⁹ Rare²⁹ 13%²⁹</td>
<td>MDM inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FGFR3</strong> mutations and fusions</td>
<td>0%²⁹ 0%²⁹ ~ 10%²⁹</td>
<td>FGFR inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TRK</strong> Fusions</td>
<td>Occasional³³ N/A</td>
<td>TRK inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total actionable mutations</strong></td>
<td>62-82%* 22-38%* Up to 89%*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Excluding IDH mutation itself
mutation (see Table 3). In addition, at least 2 patients will be identified who have actionable mutations in BRAF, EGFR, FGFR and TRK for whom existing drug access has been identified (Table 3). However, the key barriers are access to comprehensive molecular phenotyping for actionable mutations and access to appropriate drugs rather than a lack of targets.

Arguably, utilising targeted agents in glioma is the most promising new therapeutic area at this time. It is important to stress that the lack of efficacy with targeted agents to date in Table 2 is entirely in studies with unselected patients i.e. no selection to ensure that the tumour expresses the target was undertaken. In contrast, evidence that precision oncology approach of matching patients with relevant targeted therapy has been very encouraging. In GBM, the EGFR targeting antibody drug conjugate deputuzizumab mafodotin (previously known as ABT-414) in recurrent GBM was recently reported. This is the first study in recurrent GBM to show a survival benefit, with a HR of 0.68 (95% CI [0.48, 0.95]; p=0.024) and 1-year OS rates of 40% vs 28%. Importantly, our biomarker analysis of the efficacy of deputuzizumab mafodotin showed that it is only effective in patients where there is enrichment for EGFR amplification, emphasizing the importance of patient selection in using targeted agents. Similarly, this approach of targeted agents in target enriched populations in paediatric patients has been encouraging. For example, there are several reports that paediatric patients with BRAF mutated glioma have up to 39% response rates when treated with a BRAF or MEK inhibitor. Similarly, several cases in adults with a BRAF V600E GBM responding to BRAF/MEK inhibition or BRAF inhibition have been described. A noteworthy study of adults with recurrent G3 glioma treated with the BRAF inhibitor vemurafenib alone showed a response rate of 20% (1/5 patients). The TRK-inhibitor larotrectinib has also shown activity in an ETV6-NTRK3 fusion driven high grade glioma in a paediatric case. In November 2018, the FDA granted accelerated approval for targeted larotrectinib for patients with TRK gene fusions identified.

1.5 Rationale for Pilot study

The proposal for the full LUMOS concept (Section 1.2 to 1.4) is for an ambitious on-going national study, funded through a mix of funding (government, research, philanthropic and industry) and utilising cutting edge drugs and technologies as they emerge. The Pilot study aims to establish keep personnel and infrastructure to show proof of concept that this is feasible.

2. AIM AND OBJECTIVES

Aim: To perform a pilot study:
- At five Australian pilot sites and
- Demonstrate the feasibility of establishing and recruiting to the LUMOS protocol at these five sites

This pilot study will generate preliminary feasibility data to support the full study. The full LUMOS study is intended to be an on-going multi-year study funded through a mixture of grants, philanthropic and industry funding. Key to attracting this funding will be providing proof-of-concept by demonstrating that this novel and ambitious concept is feasible.

Primary objective to determine the:
1) Number of patients enrolled on study
2) Number of patients that successfully complete molecular profiling

Secondary objectives to determine the:
3) Proportion of patients that enrol on study compared to the number screened
4) Proportion of patients that successfully complete molecular profiling
5) Turn-around time (TAT) of molecular screening
6) Matching of Molecular Tumour Board recommendations with pharmaceutical agents
7) Proportion of patients in whom a molecular tumour board recommended pharmaceutical agent is obtained and used
8) Response (progression free survival) to recommended agent at 12 months
9) Number of patients who undergo further surgical debulking at time of disease progression whilst participating in LUMOS
10) Number of patients screened for the study

Tertiary and correlative objectives:

11) To study associations between clinical endpoints and potential predictive/prognostic biomarkers (tissue and circulating)

Data from the Pilot Phase will be used to inform design of the Main Study Phase. The resources and processes established for the Pilot Phase will be such that they will be readily scaled up for the Main Study Phase and allow seamless transition between the two.

3. DESIGN

This is an umbrella study wherein eligible adult patients with G2/3 gliomas are offered molecular testing to demonstrate proof of concept during this pilot stage, so that they can be treated with matched targeted agents based on the molecular profiling at the time of progression (see Study Schema) in the full study. People with progressive G2/3 gliomas who meet the trial criteria will be enrolled in the pilot. Progressive G2/3 gliomas will be defined as evidence of new contrast-enhancing tumour and/or 25% increase in the size of the T2/FLAIR area compared to prior imaging after treatment with radiotherapy and chemotherapy such as temozolomide. Patients may be recruited prior to craniotomy, allowing for collection of tissue and blood for research before and during surgery. Other patients with adequate tissue from a recent craniotomy (within 6 months of study enrolment and without any intervening treatment) can also be enrolled. Patients will then be screened for eligibility. Tissue from eligible patients will then be tested using the Illumina TruSight 170 panel. Active participation in the study will end when the patient’s Molecular Tumour Board Report from the molecular panel is provided to a Treating Physician who will continue the patient’s care.

The study will continue to closely track patients after the completion of trial for up to 2 years, with a particular emphasis on collecting data about treatments received. In addition to the Molecular Tumour Board Report, the Treating Physician will be provided with a list of known means to access targeted agents corresponding to actionable mutations found by testing with the molecular panel and described in the Molecular Tumour Board Report. It is anticipated that most patients with an actionable mutation and a matching drug will be treated by a member of the LUMOS study team as the Treating Physician although this is not mandated. Where no actionable mutations are detected or where access to a relevant targeted agent is not available, patients may be referred back their referring physician to act as the Treating Physician providing standard of care treatments.

Regardless of who the Treating Physician is, patients will be followed up regularly (see Table 4) to determine what treatments patients are receiving and the efficacy of treatment. At the time of progression, patients may be offered the option of further re-resection (if applicable) and repeat screening using the Illumina TruSight 170 panel and a new Molecular Tumour Board report will be generated.
4. STUDY POPULATION

Patients must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial. No exceptions will be made to these eligibility requirements at the time of registration. All enquiries about eligibility should be addressed by contacting the NHMRC CTC prior to registration.

4.1 Target Population

Patients with progressive G2/3 glioma after treatment with radiotherapy and chemotherapy, who consent to resection of tissue for molecular typing or analysis of tissue resected at surgery within six months prior to enrolment, with a view of treatment with matched targeted agents where available, or else treatment with standard of care therapies.

4.1.1 Inclusion Criteria

1. Adults, aged 18 years and older, with histological confirmed grade 2 or 3 glioma at initial diagnosis.

2. Prior to last craniotomy and surgery, evidence of progressive disease as defined as evidence of new contrast-enhancing tumour and/or 25% increase in the size of the T2/FLAIR area compared to prior imaging after prior treatment with radiotherapy and chemotherapy.

3. Has available tissue from resection for progressive disease for molecular profiling either within 6 months of study enrolment or following enrolment.

4. For patients who are undergoing standard of care surgery at the time of study entry:
   a. The patient must be suitable for craniotomy as the opinion of the neurosurgical team who will perform the surgery.
   b. In the opinion of the neurosurgical team, it will be possible to safely undertake a debulking procedure and that sufficient tissue will be obtained for molecular testing
   c. Has substantially recovered from their surgical resection, as evidenced by having no major on-going safety issues (e.g. infection requiring antibiotics)

5. Patients who have already undergone standard of care surgery ≤ 6 months prior to study registration, there must be sufficient tissue available for molecular testing and the patient must not have had intervening anti-cancer therapy.

6. Dose at registration must be ≤ 20mg prednisolone or ≤ 3 mg dexamethasone daily (or equivalent). Patients who are not on steroids are preferred for study participation.

7. ECOG performance status 0-2 (see Appendix 1)

8. Has measurable disease post their last craniotomy that is suitable for repeat assessment by MRI scans.

9. Willing and able to comply with all study requirements, including treatment, timing and/or nature of required assessments.

10. Signed, written informed consent (main study and tissue banking).

4.1.2 Exclusion Criteria

1. Glioma tissue for molecular pathology obtained ≥6 months prior to study entry

2. Any intervening systemic therapy or radiotherapy between most recent imaging showing progressive disease and study enrolment

3. Patients who have had intra-surgical treatments (e.g. oncolytic virus administration, Gliadel wafers) at their last craniotomy prior to study enrolment

4. Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

5. Subjects unable (e.g. due to pacemaker or ICD device) or unwilling to have a contrast-enhanced MRI of the head.
6. Serious medical or psychiatric conditions that might limit the ability of the patient to comply with the protocol.

4.2 Study Enrolment

4.2.1 Screening

Written informed consent must be signed and dated by the participant, and signed and dated by the Investigator, prior to any study-specific screening investigations being performed. All patients will undergo screening as outlined in Table 4.

Assessment for suitability to undergo craniotomy is to be determined by the treating neurosurgeon as per their institutional guidelines.

4.2.2 Registration

Registration will be done according to the instructions in the Study Manual. Once the registration process has been completed, the participant will be assigned a participant study number. Individuals may only be registered once in this trial. If participants are given the option to repeat the molecular testing at the time of progression, the same participant study number from registration must be used.

Requests for registration will only be accepted from authorised investigators at sites that have all requisite approvals in place. Registration should be done only after all screening assessments have been performed and the responsible investigator has verified the participant’s eligibility.

4.2.3 Specimen Transport to Central Laboratory for Molecular Testing

Formalin-fixed paraffin-embedded (FFPE) tumour sections are required from LUMOS patients for molecular testing. Sections are prepared from tumour blocks and sent to the study reference laboratories. Refer to the Biospecimen Screening and Sampling Manual for instructions.

5. STUDY PLAN

5.1 Molecular Phenotyping

Tissue will undergo testing at study reference laboratories with the study specified molecular panels. A Molecular Tumour Board Report will be generated based on the results of this panel. Included in this report will be a list of known Targeted Agents relevant to potential actionable mutations in the molecular panel, which will be updated on a regular basis.

Whilst it is unlikely that germline mutations will be identified with the molecular panel used in this study, in the event that this is the case, the Treating Physician will be approached to direct the patients to local familial genetics clinics.

5.2 Molecular Tumour Board

The Molecular Tumour Board Report will be reviewed by a Molecular Tumour Board Committee. A final report will be generated based on the results of the panel and contextualised with the input of the Molecular Tumour Board.

5.3 Identification of Treating Physicians

The patient will be followed and managed in the following manner after a Molecular Tumour Board Report has been delivered:

- A Treating Physician agrees to continue the care of the patient. The primary physician may be a member of the LUMOS study team, the referring physician or some other physician as nominated by the patient as their preferred treating physician.
• The Treating Physician agrees to manage the patient once delivery of a Molecular Tumour Board Report has taken place. This will include the provision of treatment for the patient’s glioma including the choice of treatment provided to the patient and the management of treatment-related monitoring (including safety and efficacy), dosing changes and toxicity management.

• The Treating Physician has been provided with a copy of the Molecular Tumour Board Report.

• The Treating Physician has been provided with information about the schedule of tests and follow up for the LUMOS study. This will include information about the possibility of repeating molecular testing at the time of progression.

5.4 **Informing patients of screening results**

All participants, including those with no ‘actionable’ biomarkers, will be informed of the results of the molecular screening of their tumour tissue by their treating clinician. The Molecular Tumour Board Report will be provided to the patient's clinician(s) for discussion with the patient.

5.5 **Discloser of clinically significant information**

Molecular screening data from this study is for research and not for clinical diagnostics. Research findings will be reviewed by the Molecular Tumour Board and other relevant expert committees as appropriate to determine clinical significance following national and international guidelines.

The molecular screening will predominantly generate information on somatic mutations in tumour tissue however pathogenic mutations, some of which may also be possible hereditary pathogenic germline mutations, may also be detected. Where such hereditary pathogenic mutations are encountered, the treating clinician will arrange, with the participant’s agreement, for referral to an appropriate familial genetics clinic and any further confirmatory testing on matched normal blood as per standard institutional practices. It is possible that clinically significant cancer-related heritable genetic factors important to future health may be identified from analysis of blood.

**Patient choice about being informed of clinically significant findings**

At the time of consent, participants will be asked to indicate if they wish to receive information on hereditary cancer risk of potential importance to their future health or that of their blood relatives. If clinically significant results are identified, the referring clinician will refer the patient to an appropriate familial genetics clinic as per standard institutional practices. No referral will be made if a participant has chosen not to be informed of clinically significant information.

5.6 **Treatment Following Delivery of Molecular Tumour Board Report**

Treatment after delivery of the Molecular Tumour Board Report is at the discretion of the Treating Physician.

5.6.1 **Follow Up Assessments**

The follow up period is a vital part of this pilot study and starts from the date of the delivery of the Molecular Tumour Board Report. All patients will be followed as shown in Table 4.

The recommended frequency of follow up visits is 2 monthly or as directed by the Treating Physician based on the schedule of the treatment received, Clinical Trial protocol, Special Access Scheme or standard of care at site. If a patient is coming in for a treatment visit or assessment, then treatment and follow up information should be reported for the LUMOS study. If the patient has transferred to another site for treatment, then this information (including MRI results) will be captured remotely.
The frequency of radiological assessments will be determined by the Treating Physician, however 8 weekly MRI assessments are recommended until progressive disease is identified by the Treating Physician or until the end of the study Follow Up period has been reached. Appendix 2 outlines the recommended MRI protocol, however response assessment will be performed as per the standard of care of the treating institution of the Treating Physician.

At the time of progressive disease on Follow Up, the study chair will be notified. Further surgery at this time will at the discretion of the Treating Physician. If sufficient tissue is available, this may be obtained for further molecular profiling and investigation of biomarkers of resistance.

5.4.2 Concomitant Medications
No specific restriction or recommendation of concomitant medications is necessary for this pilot study except as outlined in the eligibility criteria.

5.4.3 Concomitant Medication Reporting
Dexamethasone use will be recorded. No other concomitant medications will be recorded.

5.7 Study Follow Up Discontinuation
Patients will be considered to be enrolled in the study whilst they are in study follow up. Study follow up will be permanently discontinued for any of the following reasons:

- The patient declines further study follow up or withdraws their consent to participate in the study.

The reasons for discontinuing treatment will be documented in the participant's medical record and (e)CRF.

If a participant wishes to stop the study visits, they will be requested to allow their ongoing health status to be periodically reviewed via continued treatment visits or phone contact or from their general practitioner, or medical records.
6. ASSESSMENT PLAN

6.1 *Table 4: Schedule of Assessments*

<table>
<thead>
<tr>
<th>Molecular Testing Period</th>
<th>Follow up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Time from the Delivery of the Molecular Tumour Board Report)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening and Registration (Pre or within 6 months post-surgery)</td>
<td>Delivery of Molecular Tumour Board Report</td>
</tr>
<tr>
<td>Within 14 days prior to registration</td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>X</td>
</tr>
<tr>
<td>Tissue for molecular profiling</td>
<td>X</td>
</tr>
<tr>
<td>Clinic assessment</td>
<td>X</td>
</tr>
<tr>
<td>Blood tests:</td>
<td></td>
</tr>
<tr>
<td>- Haematology: FBC with differential</td>
<td></td>
</tr>
<tr>
<td>- Biochemistry: EUC, LFTs &amp; glucose</td>
<td></td>
</tr>
<tr>
<td>Brain MRI</td>
<td>X</td>
</tr>
<tr>
<td>Assessment of dexamethasone use</td>
<td>X</td>
</tr>
<tr>
<td>Blood for translational research</td>
<td>X</td>
</tr>
<tr>
<td>Pre-surgery assessment</td>
<td>X&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Determination of Treating Physician</td>
<td>X</td>
</tr>
<tr>
<td>Determination of current treatment</td>
<td>X&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Re-screening for LUMOS</td>
<td></td>
</tr>
</tbody>
</table>
1. Patients who are enrolling prior to surgery must be within 6 months of surgical resection.
2. Tissue for molecular profiling: refer to Section 4.2.3. NB Additional Fresh tissue (snap frozen) should be collected for translational research wherever possible from consenting patients as per local institutional ethics approvals.
3. As per institutional standard of care for patients undergoing craniotomy and resection of their tumour type
4. Confirmation of availability of tumour tissue from last craniotomy for molecular phenotyping and provision of the tissue to the study lab for phenotyping with study specific molecular panels
5. Aim for 28 calendar days between receipt of tissue at laboratory and delivery of final Molecular report to (a) LUMOS study team and (b) referring physician.
6. The Treating physician is the physician who will be responsible for the administration of anti-cancer treatment to the patient if appropriate. The Treating physician may be a member of the LUMOS study team, the referring physician or some other physician as nominated by the patient as their preferred treating physician. The primary physician will be responsible for the choice of treatment provided to the patient and the management of treatment-related monitoring (including safety and efficacy), dosing changes and toxicity management. The study team will meet with the patient to jointly determine who is the Treating physician and discuss arrangements for transfer of care where necessary.
7. Assessments do not need to be repeated if within 28 days of the delivery date of the Molecular Tumour Board Report to referring physician.
8. These investigations will be undertaken once the Treating Physician has been identified and prior to the patient being handed over to the care of the Treating Physician for further follow up.
9. Where patient is unable or unwilling to return for a physical study visit, these may be obtained directly from the patient, the Treating Physician or their delegate through phone, fax, email or other reasonable means of communications
10. The patient may be referred back for study re-testing at the discretion of the Treating Physician, so long as there has been evidence of progression relative to the (a) MRI at the time of commencing treatment following delivery of Molecular Tumour Board report, or (b) a subsequent MRI done after that visit, whichever is deemed most appropriate. Similarly, for translational research bloods, it is acceptable if the Treating Physician is able to organise to provide this without a patient visit. Where tissue from a subsequent resection is available, the Treating Physician will be approached to provide this.
11. Physical exam, neurological exam, ECOG performance status, weight, heart rate (HR), blood pressure (BP) and respiratory rate (RR).
12. Note that this investigation does not have to be done at the follow up time point but study team will collect information about any such testing that may have been done by the Treating Physicians since the last follow up appointment
6.2 Details of Assessments

6.2.1 Clinical Assessment
Clinical assessment includes physical examination, neurological examination, performance status, weight, blood pressure (BP) heart rate (HR) and respiratory rate (RR).

6.2.2 Imaging
MRI is the required imaging technique. Patients who are unable to undergo MRI scans will be ineligible for study participation. If a patient already on study develops a contraindication to MRI (e.g., need for implanted pacemaker or defibrillator), subsequent assessments should be performed with contrast CT scanning (or non-contrast CT if allergic to contrast).

The frequency of radiological assessments during the follow up period will be determined by the Treating Physician. However, 8 weekly MRI assessments are encouraged until progressive disease is identified or until the end of the study follow up period has been reached.

6.2.3 Blood Collection
Local pathology laboratories will be used for routine blood tests.

Central laboratories will be used to evaluate biomarkers. Participation in these studies is required.

Blood will be collected and initially processed at each site. Refer to the Biological Screening and Sampling Manual for details and procedures.

Translational research blood collection at up to 4 time points are described in Table 4:

- Screening OR pre-surgery (for patients planning to undergo surgery)
- Delivery of Molecular Tumour Board Report and Treatment Decision
- Progressive disease
- End of follow up (2 years after registration)

6.2.4 Tissue Collection
Paraffin-embedded tissue blocks will be retrieved from all patients for molecular testing at reference laboratories. Refer to the Biological Screening and Sampling Manual for procedures.

Tissue will be retrieved for translational research at the following timepoints:

- Surgery
- Progressive disease

Refer to the Study Manual for procedures, including processing of fresh tissue (e.g., snap-frozen, RNAlater) where relevant.

6.3 Follow-up After Treatment
Post-study follow up is a vital part of this pilot study. All patients will be followed as shown in Table 4.

7. OUTCOMES, ENDPOINTS AND OTHER MEASUREMENTS
This Pilot study aims to determine the feasibility of implementing the LUMOS umbrella study. Key endpoints are:
7.1 **Primary Endpoints**

7.1.1 **Number of patients enrolled**
This is defined as the absolute number of patients successfully enrolled over the lifetime of the study.

7.1.2 **Number of patient that successfully completed molecular profiling**
This is the absolute number of patients for whom molecular profiling was successfully completed over the lifetime of the study.

7.2 **Secondary Endpoints**

7.2.1 **Proportion of screened patients enrolled**
This is defined as the proportion of patients enrolled compared to those who were screened.

7.2.2 **Proportion of patients that successfully complete molecular profiling**
This is defined as the proportion of patients for whom molecular profiling was successfully completed, as a proportion of those who were enrolled.

7.2.3 **Turn-around time (TAT) of molecular screening**
This is defined as the time taken from patient consent to central receipt of a completed Molecular Tumour Board Report. In addition, the time from receipt of tumour tissue to a completed Molecular Tumour Board Report will also be measured.

7.2.4 **Matching of Molecular Tumour Board recommendations with pharmaceutical agents**
This is the absolute number of patients with actionable mutations detected on molecular profiling with targeted agents, either through a clinical trial, compassionate access, hospital supply, or pharmaceutical access programmes.

7.2.5 **The proportion of patients in whom a Molecular Tumour Board recommended pharmaceutical agent is obtained and used**
This is the proportion of patients in whom a pharmaceutical targeted agent is obtained and used, either through a clinical trial, compassionate access, hospital supply, or pharmaceutical access programmes.

7.2.6 **Response to any Molecular Tumour Board or clinician-recommended pharmaceutical agent**
Key clinical outcomes (response and duration of response, time to progression, overall survival as measured by Progression Free Survival at 12 months (PFS12)) will be recorded.

7.2.7 **Number of patients who undergo further surgical debulking at time of disease progression whilst participating in LUMOS**
This is the number of patients participating in LUMOS who are deemed suitable for second debulking surgery at the discretion of the Treating Physician.

7.2.8 **The number of patients who were screened for the study**
7.3 **Tertiary/correlative measures**

7.3.1 The associations between clinical endpoints and potential predictive/prognostic biomarkers (tissue and circulating)

Bloods and tissues, as outlined in Table 4, will be collected and stored for future investigation of resistance and identification of candidate biomarkers of clinical outcomes. These translational research studies may include but not be limited to:

- Immune cell infiltration analyses by immunohistochemistry
- Gene expression studies
- Analysis of circulating biomarkers of inflammation
- Studies that may help to understand the course of this cancer and related diseases;

Biomarkers may be RNA-based (single entity or entire expressed genome, RNA, miRNA), DNA-based (single entity or whole genome, germ line or tumour related), protein-based or other entities.

Tissue biomarkers may also be investigated as prognostic and/or predictive biomarkers of clinical endpoints. Examples may include: SMARCA4 involved in chromatin remodelling and EIF1AX a translational initiation factor.

Since the identification of new biomarkers correlating with disease activity and the efficacy or safety of treatment are rapidly evolving, the definitive list of biomarkers remains to be determined.

8. **CENTRAL REVIEW**

8.1 **Screening for eligibility**

Molecular profiling will be conducted on tumour tissue of all consenting enrolled patients. Refer to section 4.2.1 for more details.

9. **CENTRAL STORAGE OF BIOSPECIMENS**

9.1 **Central tissue collection**

Tissue will be retrieved from all participants at site and sent to the reference laboratories in Australia for molecular screening. Any remaining material will be retained for translational research. Tissue and blood samples for translational research will be sent to central laboratories for storage and translational studies (tertiary /correlative objectives). Refer to the Biological Sampling Manual for details and procedures.

9.2 **Central blood collection**

Central laboratories will be used to conduct translational studies including biomarker analyses. Blood will be collected and initially processed and stored at each site. Samples will later be shipped to a central facility for translational research and storage and translational research studies.
10. STATISTICAL CONSIDERATIONS

10.1 Sample Size
This is a pilot study and no formal sample size calculation was undertaken. It is expected that the pilot will contain 5 sites and approximately 10 patients in the 12 months period.

10.2 Statistical Analysis
The following variables will be presented using standard summary statistics. No formal statistical analysis is planned.

Recruitment:
- The number of eligible grade 2/3 glioma patients will be obtained from site screening logs and described separately at each site and overall.
- The number and percentage of these patients who are enrolled on LUMOS will be described separately at each site and overall.
- Demographic and clinical characteristics of enrolled patients will be summarised.

Molecular screening:
- The number and percentage of enrolled patients for whom tissue was successfully screened using molecular profiling.
- Reasons for not undergoing molecular screening and for unsuccessful screening.
- In patients for whom a molecular screening report is received, the median (range) time from time of consent and from time that laboratory received the tissue, to the time of receipt of the report by the Treating Physician.
- In patients for whom a molecular screening report is received, number of targets identified that match molecular targeted agents currently accessible through clinical trials or pharmaceutical access programs.
- In patients for whom a target was identified, whether or not treatment plan was subsequently changed, and reasons for changing/not changing the plan.
- In patients for whom a target was identified, the proportion who received a targeted agents as a result of the MTB recommendation.

Clinical outcomes:
- The number and percentage of enrolled patients who experience disease progression while participating on LUMOS, and the number and percentage of these who then undergo further debulking.
- The number and percentage of patients who achieve tumour response, and the median (range) duration of response.
- Overall and progression-free survival will be described using the Kaplan-Meier method.

10.3 Interim analyses
No formal interim analysis of the pilot stage will be performed, however data from the Pilot Phase will be used to inform design of the Main Study Phase. The resources and processes established for the Pilot Phase will be such that they will be readily scaled up for the Main Study Phase and allow seamless transition between the two.

11. STUDY ORGANISATION and COMMITTEES

11.1 Study coordination
The study is a locally developed and led investigator initiated collaborative group study by the COGNO group. Coordination, monitoring, data acquisition and management and statistical analysis will be performed by the NHMRC CTC.
11.2 Trial Management Committee

The Trial Management Committee (TMC) will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees).

Progress and safety data for all patients will be monitored by the TMC. There are no interim analyses planned for this trial. An independent safety data monitoring committee is not required or planned for this pilot assessing feasibility of molecular profiling.

11.3 Molecular Tumour Board Committee

The Molecular Tumour Board Committee will oversee the molecular pathology requirements of this study.

12. ADMINISTRATIVE ASPECTS

12.1 Ethics and regulatory compliance

In Australia, the study will be conducted according to the Note for Guidance on Good Clinical Practice (Integrated Addendum to ICH E6 (R1): Guidelines for Good Clinical Practice ICH E6(R2) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC National Statement on Ethical Conduct in Human Research 2007 (updated 2018 and amended from time to time), the NHMRC Australian Code for the Responsible Conduct of Research 2018 (and as amended from time to time), and the principles laid down by the World Medical Association in the Declaration of Helsinki 2013.

To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the patient has provided written informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a participant. In this circumstance the NHMRC CTC, principal investigator and HREC must be advised immediately.

12.2 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the NHMRC CTC, University of Sydney and will only be available to people directly involved with the study.

12.3 Protocol amendments

Changes and amendments to the protocol can only be made by the Trial Management Committee. Approval of amendments by the Institutional HREC is required prior to their implementation. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the data collected, if required, will be incorporated in the amendment.

The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial participant(s).

12.4 Data Handling and Record Keeping

All trial data required for the monitoring and analysis of the study will be recorded on the (e)CRFs provided. All required data entry fields must be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated.
Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a participant's medical records, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator’s record of a participant's study-related data.

The following information should be entered into the participant's medical record:

a. The participant's protocol identification.

b. The date that the participant entered the study, and participant number.

c. A statement that informed consent was obtained (including the date)

d. Relevant medical history

e. Dates of all participant visits and results of key trial parameters.

f. The date the participant exited the study, and a notation as to whether the participant completed the study or reason for discontinuation.

All study-related documentation at ANZ sites will be maintained for 15 years following completion of the study.

12.5 Study Monitoring

Data from this study will be monitored by Clinical Trials Program staff from the NHMRC CTC or their delegates. Monitoring will include centralised review of CRFs and other study documents for protocol compliance, data accuracy and completeness. Monitoring may include monitoring visits to investigational sites during the study for source data verification, review of the investigator’s site file and drug handling records. The NHMRC CTC will be given direct access to source documents, CRFs and other study-related documents. By signing the informed consent form, the participant gives authorised NHMRC CTC staff direct access to their medical records and the study data.

12.6 Audit and Inspection

This study may be participant to audit or inspection by representatives of the COGNO, the CTC or representatives of regulatory bodies (e.g. Therapeutic Goods Administration (TGA) once the study progresses beyond the pilot phase and includes investigational treatment arms).

12.7 Clinical Study Report

A Clinical Study Report which summarises and interprets all the pertinent study data collected will be issued which may form the basis of a manuscript intended for publication.

12.8 Publication Policy

The Trial Management Committee will appoint a Writing Committee to draft manuscript(s) based on the trial data. Manuscript(s) will be submitted to peer-reviewed journal(s). The first publication will be the report of the full trial results based on the main protocol generally using the study group name for large Phase I/III studies, with subsequent publications of data subsets in individual names based on contribution. The Writing Committee will develop a publication plan, including authorship, target journals and expected dates of publication. All publications must receive prior written approval from the TMC prior to submission. Authorship will follow the recommendations of the ICMJE.

13. PROTOCOL AMENDMENTS

<table>
<thead>
<tr>
<th>Amendment no.</th>
<th>Date</th>
<th>Summary of change</th>
</tr>
</thead>
</table>

LUMOS protocol, COGNO 19/05, CTC0267 Confidential
Version 1.2 dated 13 November 2019 Page 27 of 33
14. REFERENCES


## 15. APPENDICES

### 15.1 Appendix 1: ECOG Performance Status

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>
### 15.2 Appendix 2: Recommended MRI Protocol

For sites that do NOT have advanced imaging available: (FDA/NBTS/NCI Standardized MRI Protocol).

#### 3T Protocol:

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Ax FLAIR</th>
<th>Ax DWI</th>
<th>3D T1 Pre</th>
<th>Ax T2</th>
<th>3D T1 Post&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial</td>
<td>TSE&lt;sup&gt;c&lt;/sup&gt; (turbo dark fluid)</td>
<td>EPI&lt;sup&gt;f&lt;/sup&gt;</td>
<td>MPRAGE&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>TSE&lt;sup&gt;c&lt;/sup&gt;</td>
<td>MPRAGE&lt;sup&gt;d,e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plane</td>
<td>Axial</td>
<td>Axial</td>
<td>Axial/Sagittal</td>
<td>Axial</td>
<td>Axial/Sagittal</td>
</tr>
<tr>
<td>Mode</td>
<td>2D</td>
<td>2D</td>
<td>3D</td>
<td>2D</td>
<td>3D</td>
</tr>
<tr>
<td>TR [ms]</td>
<td>&gt;6000</td>
<td>&gt;5000</td>
<td>2100&lt;sup&gt;g&lt;/sup&gt;</td>
<td>&gt;2500</td>
<td>2100&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>TE [ms]</td>
<td>100-140</td>
<td>Min</td>
<td>Min</td>
<td>80-120 Min</td>
<td></td>
</tr>
<tr>
<td>TI [ms]</td>
<td>2500</td>
<td></td>
<td>1100&lt;sup&gt;h&lt;/sup&gt;</td>
<td>90/≥160 10-15</td>
<td></td>
</tr>
<tr>
<td>Flip Angle</td>
<td>90/≥160</td>
<td>90/180</td>
<td>10-15</td>
<td>90/≥160</td>
<td>10-15</td>
</tr>
<tr>
<td>Frequency</td>
<td>≥256</td>
<td>128</td>
<td>256</td>
<td>≥256 256</td>
<td></td>
</tr>
<tr>
<td>Phase</td>
<td>≥256</td>
<td>128</td>
<td>256</td>
<td>≥256 256</td>
<td></td>
</tr>
<tr>
<td>NEX</td>
<td>≥1</td>
<td>≥1</td>
<td>≥1</td>
<td>≥1    ≥1</td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>A/P</td>
<td>R/L</td>
<td>A/P</td>
<td>A/P   A/P</td>
<td></td>
</tr>
<tr>
<td>Direction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOV</td>
<td>240mm</td>
<td>240mm</td>
<td>256mm (for 1mm isotropic)</td>
<td>240mm</td>
<td>256mm (for 1mm isotropic)</td>
</tr>
<tr>
<td>Slice Thickness</td>
<td>3mm</td>
<td>3mm</td>
<td>1mm</td>
<td>3mm   1mm</td>
<td></td>
</tr>
<tr>
<td>Gap/Spacing</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0     0</td>
<td></td>
</tr>
<tr>
<td>Diffusion Options</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parallel Imaging</td>
<td>Up to 2x</td>
<td>Up to 2x</td>
<td>Up to 2x</td>
<td>Up to 2x</td>
<td></td>
</tr>
<tr>
<td>Scan Time (Approx)</td>
<td>4-5 min</td>
<td>3-5 min</td>
<td>5-8 min</td>
<td>3-5 min 5-8 min</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> 0.1 mmol/kg or up to 20cc (single, full dose) of MR contrast.
<sup>b</sup> Post-contrast 3D axial T1-weighted images should be collected with identical parameters to pre-contrast 3D axial T1-weighted images.
<sup>c</sup> TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba).
<sup>d</sup> MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) is equivalent to the inversion recovery SPGR (IR-SPGR or Fast SPGR with inversion activated; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).
<sup>e</sup> A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.
<sup>f</sup> In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option.
<sup>g</sup> For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.

<sup>h</sup> For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.
Acronyms:
Ax = Axial; ADC = apparent diffusion coefficient. FLAIR = fluid attenuated inversion recovery; DWI = diffusion-weighted imaging; 3D = three dimensional; TSE = turbo spin echo; EPI = echo planar imaging; MPRAGE = magnetization prepared rapid gradient-echo; A/P = anterior to posterior; R/L = right to left; NEX = number of excitations or averages; FOV = field of view

1.5T Protocol:

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Ax FLAIR</th>
<th>Ax DWI</th>
<th>3D T1 Pre</th>
<th>Ax T2</th>
<th>3D T1 Post(b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plane</td>
<td>Ax</td>
<td>Ax</td>
<td>Sagittal/Axial</td>
<td>Axial</td>
<td>Sagittal/Axial</td>
</tr>
<tr>
<td>Mode</td>
<td>2D</td>
<td>2D</td>
<td>3D</td>
<td>2D</td>
<td>3D</td>
</tr>
<tr>
<td>TR [ms]</td>
<td>&gt;6000</td>
<td>&gt;5000</td>
<td>2100(g)</td>
<td>&gt;3500</td>
<td>2100(g)</td>
</tr>
<tr>
<td>TE [ms]</td>
<td>100-140</td>
<td>Min</td>
<td>Min</td>
<td>100-120</td>
<td>Min</td>
</tr>
<tr>
<td>TI [ms]</td>
<td>2200</td>
<td>1100(h)</td>
<td></td>
<td></td>
<td>1100(h)</td>
</tr>
<tr>
<td>Flip Angle</td>
<td>90/(\geq160)</td>
<td>90/180</td>
<td>10-15</td>
<td>90/180</td>
<td>10-15</td>
</tr>
<tr>
<td>Frequency</td>
<td>256</td>
<td>128</td>
<td>172(i)</td>
<td>256</td>
<td>172(i)</td>
</tr>
<tr>
<td>Phase</td>
<td>256</td>
<td>128</td>
<td>172(i)</td>
<td>256</td>
<td>172(i)</td>
</tr>
<tr>
<td>NEX</td>
<td>(\geq1)</td>
<td>(\geq1)</td>
<td>(\geq1)</td>
<td>(\geq1)</td>
<td>(\geq1)</td>
</tr>
<tr>
<td>Frequency Direction</td>
<td>A/P</td>
<td>R/L</td>
<td>A/P</td>
<td>A/P</td>
<td>A/P</td>
</tr>
<tr>
<td>FOV</td>
<td>240mm</td>
<td>240mm</td>
<td>256mm</td>
<td>240mm</td>
<td>256mm</td>
</tr>
<tr>
<td>Slice Thickness</td>
<td>(\leq4mm)</td>
<td>(\leq4mm)</td>
<td>(\leq1.5mm)</td>
<td>(\leq4mm)</td>
<td>(\leq1.5mm)</td>
</tr>
<tr>
<td>Gap/Spacing</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diffusion Options(d)</td>
<td></td>
<td>(b = 0, 500, and 1000)</td>
<td>(s/mm^2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parallel Imaging</td>
<td>Yes-If Available</td>
<td>Yes-If Available</td>
<td>Yes-If Available</td>
<td>Yes-If Available</td>
<td>Yes-If Available</td>
</tr>
<tr>
<td>Scan Time (Approx)</td>
<td>4-5 min</td>
<td>3-5 min</td>
<td>5-8 min</td>
<td>3-5 min</td>
<td>5-8 min</td>
</tr>
</tbody>
</table>

\(a\) 0.1 mmol/kg or up to 20cc (single, full dose) of MR contrast.
\(b\) Post-contrast 2D axial T1-weighted images should be collected with identical parameters to pre-contrast 2D axial T1-weighted images
\(c\) TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)
\(d\) MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) is equivalent to the inversion recovery SPGR (IR-SPGR or Fast SPGR with inversion activated; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).
\(e\) A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.
\(f\) In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option.
\(g\) For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.
\(h\) For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.
Older model MR scanners that are not capable of >2 b-values should use $b = 0$ and 1000 s/mm$^2$.

Acronyms:
Ax = Axial; ADC = apparent diffusion coefficient. FLAIR = fluid attenuated inversion recovery; DWI = diffusion-weighted imaging; 3D = three dimensional; TSE = turbo spin echo; EPI = echo planar imaging; MPRAGE = magnetization prepared rapid gradient-echo; A/P = anterior to posterior; R/L = right to left; NEX = number of excitations or averages; FOV = field of view