

# BMJ Open LUMOS - Low and Intermediate Grade Glioma Umbrella Study of Molecular Guided Therapies at relapse: Protocol for a pilot study

Benjamin Y Kong <sup>1,2</sup>, Hao-Wen Sim,<sup>1,3,4,5</sup> Anna K Nowak,<sup>6,7</sup> Sonia Yip,<sup>1</sup> Elizabeth H Barnes,<sup>1</sup> Bryan W Day,<sup>8,9</sup> Michael E Buckland,<sup>10</sup> Roel Verhaak,<sup>11</sup> Terrance Johns,<sup>12</sup> Cleo Robinson,<sup>13</sup> Marc A Thomas,<sup>13</sup> Tindaro Giardina,<sup>13</sup> Zarnie Lwin,<sup>14,15</sup> Andrew M Scott,<sup>16,17,18,19</sup> Jonathon Parkinson,<sup>20</sup> Rosalind Jeffree,<sup>21,22</sup> Richard de Abreu Lourenco,<sup>23</sup> Elizabeth J Hovey,<sup>24,25</sup> Lawrence M Cher,<sup>26</sup> Ganessan Kichendasse,<sup>27,28</sup> Mustafa Khasraw,<sup>29</sup> Merryn Hall,<sup>1</sup> Emily Tu,<sup>1</sup> Benhur Amanuel,<sup>13</sup> Eng-Siew Koh,<sup>25,30,31</sup> Hui K Gan<sup>17,18,19,32</sup>

**To cite:** Kong BY, Sim H-W, Nowak AK, *et al.* LUMOS - Low and Intermediate Grade Glioma Umbrella Study of Molecular Guided Therapies at relapse: Protocol for a pilot study. *BMJ Open* 2021;**11**:e054075. doi:10.1136/bmjopen-2021-054075

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-054075>).

Received 02 June 2021  
Accepted 02 December 2021



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

## Correspondence to

Dr Benjamin Y Kong;  
[ben.kong@sydney.edu.au](mailto:ben.kong@sydney.edu.au)

## ABSTRACT

**Introduction** Grades 2 and 3 gliomas (G2/3 gliomas), when combined, are the second largest group of malignant brain tumours in adults. The outcomes for G2/3 gliomas at progression approach the dismal outcomes for glioblastoma (GBM), yet there is a paucity of trials for Australian patients with relapsed G2/3 gliomas compared with patients with GBM. LUMOS will be a pilot umbrella study for patients with relapsed G2/3 gliomas that aims to match patients to targeted therapies based on molecular screening with contemporaneous tumour tissue. Participants in whom no actionable or no druggable mutation is found, or in whom the matching drug is not available, will form a comparator arm and receive standard of care chemotherapy. The objective of the LUMOS trial is to assess the feasibility of this approach in a multicentre study across five sites in Australia, with a view to establishing a national molecular screening platform for patient treatment guided by the mutational analysis of contemporaneous tissue biopsies

**Methods and analysis** This study will be a multicentre pilot study enrolling patients with recurrent grade 2/3 gliomas that have previously been treated with radiotherapy and chemotherapy at diagnosis or at first relapse. Contemporaneous tumour tissue at the time of first relapse, defined as tissue obtained within 6 months of relapse and without subsequent intervening therapy, will be obtained from patients. Molecular screening will be performed by targeted next-generation sequencing at the reference laboratory (PathWest, Perth, Australia). RNA and DNA will be extracted from representative formalin-fixed paraffin embedded tissue scrolls or microdissected from sections on glass slides tissue sections following a review of the histology by pathologists. Extracted nucleic acid will be quantified by Qubit Fluorometric Quantitation (Thermo Fisher Scientific). Library preparation and targeted capture will be performed using the TruSight Tumor 170 (TST170) kit and samples sequenced on NextSeq 550 (Illumina) using NextSeq V.2.5 hi output reagents, according to the manufacturer's instructions.

## Strengths and limitations of this study

- This study will prospectively investigate the feasibility and utility of contemporaneous molecular profiling in patients with relapsed grades 2 and 3 gliomas to identify targetable mutations and potential matched drugs.
- This pilot study will also establish the feasibility of integrating multidisciplinary discussion of individual patients into tumour sequencing workflows, supporting a larger clinical trial.
- A molecular tumour advisory panel consisting of a multidisciplinary committee with neuro-oncology expertise will provide the most appropriate treatment recommendations, tailored to drug availability and eliminating superfluous information.
- Profiling of tissue at diagnosis and relapse will provide additional information about molecular evolution that occurs over time in lower grade glioma.

Data analysis will be performed using the Illumina BaseSpace TST170 app v1.02 and a custom tertiary pipeline, implemented within the Clinical Genomics Workspace software platform from PierianDx (also refer to section 3.2). Primary outcomes for the study will be the number of patients enrolled and the number of patients who complete molecular screening. Secondary outcomes will include the proportion of screened patients enrolled; proportion of patients who complete molecular screening; the turn-around time of molecular screening; and the value of a brain tumour specific multi-disciplinary tumour board, called the molecular tumour advisory panel as measured by the proportion of patients in whom the treatment recommendation was refined compared with the recommendations from the automated bioinformatics platform of the reference laboratory testing.

**Ethics and dissemination** The study was approved by the lead Human Research Ethics Committee of the Sydney Local Health District: Protocol No. X19-0383. The study

will be conducted in accordance with the principles of the Declaration of Helsinki 2013, guidelines for Good Clinical Practice and the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007, updated 2018 and as amended periodically). Results will be disseminated using a range of media channels including newsletters, social media, scientific conferences and peer-reviewed publications.

**Trial registration number** ACTRN12620000087954; Pre-results.

## INTRODUCTION

Primary brain tumours are rare cancers, ranking as the 15th most common cancer by incidence in Australia in 2017.<sup>1</sup> Despite their relative rarity, brain tumours have a large impact on mortality and morbidity, particularly in adolescents and young adult (AYA) patients aged 15–24 years, for whom they represent the leading cause of cancer related mortality. The most common type of primary brain tumour (~45% of primary brain tumours) is grade 4 glioma (glioblastoma), which is associated with the shortest overall survival (OS).

Grades 2 and 3 gliomas (G2/3 gliomas) are the second largest group of malignant brain tumours in adults, making up approximately 17% of all primary brain tumours.<sup>1 2</sup> They consist of G2 gliomas (low grade) and G3

gliomas (intermediate grade). The latter group (G3) have historically been classified together with high grade gliomas, some colloquial reference to them as ‘intermediate’ grade occurs given their distinct natural history and treatment compared with grade 4 gliomas (high grade).<sup>3</sup> The recently revised WHO CNS5 classification would upgrade some histological G2/3 gliomas to grade 4, based on their molecular characteristics, giving them an integrated diagnosis of glioblastoma.<sup>4</sup> The historical definition of G2/3 gliomas has been used to enable comparison with already completed studies. Hereafter, we will refer to the G2 and G3 gliomas collectively as ‘lower grade’ gliomas for the sake of brevity. Adjuvant treatment of newly diagnosed high risk G2 gliomas with radiotherapy and chemotherapy results in significant improvements in OS<sup>5</sup> while adjuvant radiotherapy and chemotherapy improves survival in high-grade glioma such as anaplastic oligodendroglioma<sup>6</sup> or glioblastoma<sup>7</sup> (table 1). For G2 gliomas as a whole, the addition of procarbazine, CCNU (lomustine) and vincristine (PCV) chemotherapy to radiotherapy improves the median OS from 7.8 to 13.3 years (HR 0.59).<sup>5</sup> Oligodendrogliomas are particularly sensitive to chemotherapy and the addition of adjuvant PCV to RT alone in G3 oligodendrogliomas results in a significant

**Table 1** Standard adjuvant treatment and survival of glioma subtypes at diagnosis

Nomenclature (WHO 2016)	Overlapping nomenclature (WHO 2021)	Molecular characteristics	First line treatment following maximal safe resection	Median overall survival from diagnosis
Glioblastoma, IDH-wildtype WHO (2016) grade IV	Glioblastoma, IDH – wildtype, CNS WHO grade 4	IDH wild-type	Chemoradiotherapy with subsequent temozolomide	~15 months <sup>7</sup>
Anaplastic astrocytoma, IDH-wildtype, WHO (2016) grade III	Glioblastoma, IDH – wildtype, CNS WHO grade 4	IDH wild-type	Chemoradiotherapy with subsequent temozolomide	~20 months <sup>26</sup>
Anaplastic astrocytoma, IDH-mutant, WHO (2016) grade III	Astrocytoma, IDH-mutant, CNS WHO grade 3	IDH mutated 1p19q non-co-deleted	Radiotherapy with subsequent temozolomide	~5 years <sup>26</sup>
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q codeleted, WHO (2016) grade III	Oligodendroglioma, IDH-mutant, and 1p/19q co-deleted, CNS WHO grade 3	IDH mutated 1p19q co-deleted	Radiotherapy then PCV chemotherapy	>11 years <sup>26</sup>
Diffuse astrocytoma, IDH-wildtype, WHO (2016) grade II	Glioblastoma, IDH-wildtype, CNS WHO grade 4 (in some cases)	IDH wild-type	Consider radiotherapy followed by chemotherapy	~5 years <sup>26</sup>
Diffuse astrocytoma, IDH-mutant, WHO (2016) grade II (high risk)	Astrocytoma, IDH-mutant, CNS WHO grade 2	IDH mutated 1p19q non-co-deleted	Radiotherapy then PCV chemotherapy	~8 years <sup>26</sup>
Oligodendroglioma, IDH-mutant and 1p/19q codeleted, WHO (2016) grade II (high risk)	Oligodendroglioma, IDH-mutant and 1p/19q co-deleted, CNS WHO grade 2	IDH mutated 1p19q co-deleted	Radiotherapy then PCV chemotherapy	>12 years <sup>26</sup>

High-risk features include  $\geq 3$  variables; age  $\geq 40$ , astrocytoma histology, tumours  $\geq 6$  cm, tumour crossing midline or preoperative neurological deficits (not seizure).<sup>27</sup> A comparison with the updated WHO 2021 CNS5 classification is made although this was not published at the time of study initiation.<sup>4</sup> IDH-wild-type grade 3 astrocytoma is frequently associated with molecular features of glioblastoma.<sup>5 28</sup> CNS, Central nervous system; IDH, Isocitrate dehydrogenase; PCV, procarbazine, CCNU (lomustine), vincristine.

**Table 2** Summary of benefit from systemic therapy of G2/3 gliomas at relapse

	G2 gliomas	G3 gliomas	Mixed G2 and G3	All three groups Median (range)
<b>Post-radiotherapy but no prior systemic therapy</b>				
Chemo <sup>8-10</sup>	RR: 27% <sup>29</sup> mPFS: 10mo <sup>29</sup> PFS6: 67% <sup>11</sup> PFS12: N/A mOS: 14mo <sup>29</sup> OS12: N/A OS24: N/A	RR: 44%–63% <sup>8 9</sup> mPFS: 7-10mo <sup>8 9</sup> PFS6: N/A PFS12: N/A mOS: 16-20mo <sup>8 9</sup> OS12: N/A OS24: N/A	RR: 54% <sup>11</sup> mPFS: 8mo <sup>11</sup> PFS6: 67% <sup>11</sup> PFS12: 25% <sup>11</sup> mOS: 14mo <sup>11</sup> OS12: 60% <sup>11</sup> OS24: 23% <sup>11</sup>	RR: 49% (27–63) mPFS: 9mo (7–10) mOS: 15mo (14–20)
<b>Pre-treated with radiotherapy and systemic therapy</b>				
Chemo <sup>30-32</sup>	RR: 47% <sup>33</sup> mPFS: 10mo <sup>33*</sup> PFS6: 76% <sup>33</sup> PFS12: 39% <sup>33*</sup> mOS: N/A OS6 N/A	RR: 13%–23% <sup>30-32</sup> mPFS: 4-8mo <sup>30-32</sup> PFS6: 30%–40% <sup>30 31</sup> PFS12: 5%–8% <sup>30 31</sup> mOS: 7-19mo <sup>30 31</sup> OS12: 23% <sup>31</sup>	N/A	RR: 23% (13–47) mPFS: 6mo (4–10) PFS6: 40% (30–76) mOS: 8 mo (7–19)
Targeted ± Chemo <sup>33-37</sup>	RR: 0 <sup>36*</sup> mPFS: 11mo <sup>36*</sup> PFS6: N/A PFS12: 39% <sup>36*</sup> mOS: N/A OS6 94% <sup>36*</sup>	RR: 0-10 <sup>34 37</sup> mPFS: 2-3mo <sup>34 37</sup> PFS6: 24% <sup>34</sup> PFS12: 14% <sup>34</sup> mOS: 2-8mo <sup>34 37</sup> OS6: N/A	RR: 0%–8% <sup>35 36</sup> mPFS: 2–11mo <sup>35 36</sup> PFS6: 15% <sup>35</sup> PFS12: N/A mOS: 7mo <sup>35</sup> OS6: 20% <sup>35</sup>	RR: 0% (0–10) mPFS: 3mo (2–11) PFS6 20% (15–24) mOS: 7mo (2–8)
Bevacizumab monotherapy <sup>38 39</sup>	N/A	RR: 43%–64% <sup>38 39</sup> mPFS: 3-7mo <sup>38 39</sup> PFS6: 21% <sup>38</sup> mOS: 9–12 mo <sup>38 39</sup> OS6: 76% <sup>39</sup> OS12: 36% <sup>39</sup>	N/A	RR: 54% (0–10) mPFS: 5mo (3–7) mOS: 11mo (9–12)
Comments:	Chemo: TMZ, <sup>10 12 33</sup> hydroxyurea <sup>36</sup> Targeted: erlotinib, <sup>37</sup> imatinib <sup>36</sup>	Chemo: TMZ, <sup>8</sup> PCV, <sup>9</sup> cyclophosphamide, <sup>32</sup> irinotecan, <sup>31</sup> paclitaxel, <sup>30</sup> hydroxyurea <sup>34</sup> Targeted: imatinib <sup>34</sup>	Chemo: CCNU, <sup>35</sup> hydroxyurea <sup>36</sup> Targeted: sunitinib, <sup>35</sup> imatinib <sup>36</sup>	

\*These studies contained approximately two-thirds patients without prior systemic therapy.

CCNU, Lomustine; mOS, median overall survival; mPFS, median progression-free survival; N/A, not available; PCV, procarbazine, CCNU and vincristine; RR, response rate; TMZ, temozolomide.

improvement in median OS from 7.3 years to 14.7 years (HR 0.59). The definition of oligodendroglioma in clinical trials has evolved over time from a histological to molecular definition based on 1p/19q co-deletion. For patients with G3 anaplastic glioma without a 1p/19q deletion, the addition of adjuvant temozolomide (TMZ) results in an even greater relative OS improvement.

Despite the relatively favourable overall prognosis of newly diagnosed G2/3 gliomas, the outcomes for G2/3 gliomas at the time of relapse following standard treatment approach those of glioblastoma; the median progression-free survival (PFS) is 9 months and median OS 15 months.<sup>8-11</sup> Furthermore, the limited data on patients with relapse suggest that OS is minimally affected by the histology at diagnosis (table 2). Patients with relapsed G2/3 gliomas can experience highly symptomatic relapses, characterised by seizures together with cognitive and functional impairment.<sup>12</sup> In this setting, there is no accepted standard of care treatment although common

chemotherapeutic regimens that are used include PCV, TMZ, CCNU/carmustine or other platinum-based regimens depending on prior chemotherapy exposure.

### Rationale for umbrella trial design

LUMOS is an umbrella study that will screen G2/3 glioma patients with relapsed disease for actionable tumour mutations that are matched to targeted drugs. Given the diversity of targets in G2/3 gliomas (table 3), the umbrella trial design was chosen to efficiently test a range of targeted drugs. The requirement to screen patients who have contemporaneous tissue available will ensure that molecular targets identified during screening will accurately reflect the expected targets within the tumour at the time of receiving treatment. This study design will minimise the possibility that genomic or epigenetic evolution has occurred between the time of initial biopsy and disease relapse, thus rendering targeted therapies ineffective.<sup>13</sup>



**Table 3** Potential drug therapies by mutation status in the LUMOS study

Gene mutation	IDH mutated, 1 p/19q co-deleted	IDH mutated, 1 p/19q intact	IDH wild-type	Potential targeted drugs
IDH mutation	100%	100%	0%	Multiple including IDH inhibitors, IDH vaccines, PARP inhibitors, immunotherapy
BRAF amplification	39% <sup>40</sup>	2% <sup>40</sup>	17% <sup>40</sup>	RAF inhibitors, MEK inhibitors
PIK3CA mutation	4%–20% <sup>17 41</sup>	5% <sup>41</sup>	2%–9% <sup>17 41</sup>	PI3K inhibitors
PIK3R1 mutation	9% <sup>17</sup>	Occasional <sup>17</sup>	Rare <sup>17</sup>	PI3K inhibitors
EGFR amplification or mutation	6% <sup>41</sup>	15% <sup>41</sup>	27%–89% <sup>17 41</sup>	EGFR inhibitors or EGFR ADCs
BRAF V600E mutation	1%–5% <sup>42</sup>	0% <sup>42</sup>	0% <sup>17</sup>	BRAF inhibitors, MEK inhibitors
PTEN inactivating mutation	2% <sup>41</sup>	0% <sup>41</sup>	20%–23% <sup>17 41</sup>	PI3K inhibitors
PDGFRA amplification	~1% <sup>17</sup>	0–16 <sup>17</sup>	0%–28% <sup>17</sup>	Multi-kinase inhibitors that include PDGFR
CDK4 amplification	Rare <sup>17</sup>	Rare <sup>17</sup>	7% <sup>17</sup>	CDK4/6 inhibitors
MDM4 amplification	0% <sup>17</sup>	Rare <sup>17</sup>	13% <sup>17</sup>	MDM inhibitors
FGFR3 mutations and fusions	0% <sup>17</sup>	0% <sup>17</sup>	~10% <sup>17</sup>	FGFR inhibitors
TRK Fusions	Occasional <sup>43</sup>	N/A	N/A	TRK inhibitors
Total actionable mutations	62%–82%*	22%–38%*	Up to 89%*	

\*Excluding IDH mutation itself.

ADC, antibody drug conjugate; EGFR, Epidermal growth factor receptor; FGFR, Fibroblast growth factor receptor; IDH, Isocitrate dehydrogenase; MDM, Murine double minute; MEK, MAP kinase or ERK kinase; N/A, not available; PARP, Poly ADP ribose polymerase; PDGFR, Platelet-derived growth factor receptor; TRK, Tropomyosin receptor kinase.

Given the poor prognosis of patients with progressive or recurrent tumours, the better tolerability of targeted agents over chemotherapy and the potential to discover clinical activity of existing drugs in novel indications, the LUMOS study design is expected to be attractive to both patients and clinicians alike.

### Feasibility and role of resection at relapse for grade 2/3 gliomas

Resection of tumour at the time of disease relapse is considered feasible in the majority of patients with recurrent lower grade gliomas.<sup>14</sup> In previous studies performed prior to the routine use of post-operative adjuvant therapy at initial diagnosis, gross total resection was achieved in up to 50% of patients and the addition of adjuvant therapy led to a significant improvement in PFS compared with surgery alone.<sup>15</sup>

Pathological information gleaned from resection of tumour of an individual patient reveals that tumour biology is significantly altered in recurrent tumours due to clonal selective pressures generated by current therapies,<sup>13</sup> with transformation to higher grade gliomas (grade 3 or 4) occurring in 25% of cases. Furthermore, radiological enhancement alone is a poor predictor of malignant progression.<sup>16</sup>

### Molecular drug targets in recurrent glioma

Routine testing for molecular aberrations consists of isocitrate dehydrogenase (IDH) mutations and 1p/19q

codeletion in most centres, with variable access to *ATRX* mutations and *TP53* testing. Individual mutations are present at a low prevalence in G2/3 gliomas; however, the large number of potentially actionable mutations collectively result in a large proportion of patients having an actionable mutation.<sup>17</sup> Potential druggable genetic mutations are shown in [table 3](#).

## METHODS AND ANALYSIS

### Eligibility

The inclusion and exclusion criteria for the study are listed in [box 1](#).

### Study plan

#### Molecular phenotyping to generate molecular pathology report

Tumour tissue resected at surgery will undergo testing at a single study reference laboratory using the Illumina TruSight 170 molecular screening panel, capable of detecting the somatic mutation profile of 170 genes, SNV, indel (151 genes), copy number abnormalities (59 genes) and gene fusion and splice variants (55 genes).<sup>18–20</sup> The planned duration of recruitment for the study was between 1 May 2020 and 31 May 2021.

A commercial bioinformatics pipeline (Illumina NextSeq 550 RTA2) will be used to perform base calling and quality scoring. Next-generation sequencing (NGS) data analysis will be performed using a commercial

**Box 1 Inclusion and exclusion criteria**
**Inclusion criteria**

- Adults aged 18 years and older, with histologically confirmed grade 2/3 glioma at initial diagnosis.
- Prior to last craniotomy and surgery, evidence of progressive disease defined by new contrast-enhancing tumour and/or 25% increase in T2/FLAIR area compared with prior imaging after prior treatment with radiotherapy and chemotherapy.
- Contemporaneous tissue available from resection for progressive disease either within 6 months of study enrolment or following enrolment.
- For patients undergoing standard of care surgery at the time of study entry:
  - Suitable for craniotomy in the opinion of the treating neurosurgeon.
  - In the opinion of the neurosurgeon, it is possible to safely undertake a debulking procedure and sufficient tissue will be obtained for molecular profiling.
  - Has substantially recovered from surgical resection, as evidenced by having no ongoing safety issues (e.g., postoperative infection).
- For patients who have already undergone standard of care surgery  $\leq 6$  months prior to study entry
  - Sufficient tissue must be available for molecular testing.
  - The patient must not have had intervening anticancer therapy.
- Dose at registration  $\leq 20$  mg prednisolone or  $\leq 3$  mg dexamethasone daily (or equivalent).
- ECOG performance status 0–2.
- Measurable disease after last craniotomy that is suitable for repeat assessment by MRI.
- Willing and able to comply with all study requirements.
- Signed, written informed consent.

**Exclusion criteria**

- Glioma tissue for molecular profiling obtained  $\geq 6$  months prior to study entry.
- Intervening systemic therapy (chemotherapy, targeted and/or immune checkpoint inhibitors) or radiotherapy between most recent imaging showing disease progression and study enrolment.
- Administration of intrasurgical treatments (local therapies, carmustine wafers, focused ultrasound, oncolytic viruses, convection enhanced delivery) at last craniotomy prior to study enrolment.
- Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or impair the ability of the subject to receive protocol therapy or the ability of the patient to comply with the protocol.
- Subjects unable (or unwilling) to have a contrast enhanced MRI of the head.
- Serious medical or psychiatric conditions that might limit the ability of the patient to comply with the protocol.

secondary bioinformatics pipeline (Illumina's BaseSpace TST170 app V.1.02) for somatic variant, copy number variant, splice variant and gene fusion analysis. This platform is not validated for assessment of tumour mutational burden or histone mutations. A commercial tertiary bioinformatics platform (Clinical Genomics Workspace software platform from PierianDx ([www.pierianDX.com](http://www.pierianDX.com))) will be used to generate quality control metrics and to identify and classify DNA/RNA alterations using databases including but not limited to: Genomic Build GRCh37, p13, Genomic Annotation Sources NCBI RefSeq V.105,

**Box 2 LUMOS study endpoints**
**Primary endpoints:**

- ▶ Number of patients enrolled.
- ▶ Number of patients that successfully completed molecular screening.

**Secondary endpoints**

- ▶ Proportion of screened patients enrolled.
- ▶ Proportion of patients that successfully completed molecular screening.
- ▶ Turnaround time of molecular screening.
- ▶ Matching of molecular tumour advisory panel recommendations with pharmaceutical agents.
- ▶ The proportion of patients in whom an MTAP recommended pharmaceutical agent is obtained and used.
- ▶ Response to any MTAP or physician-recommended pharmaceutical agent.
- ▶ Number of patients who undergo further surgical debulking at time of disease progression while on the study.
- ▶ The number of patients who were screened for the study.

**Tertiary endpoints**

- ▶ Association between clinical endpoints and predictive/prognostic biomarkers.

NHLBI ESP V.0.0.30, dbSNP 149, COSMIC V.84, ddNSFP 3.0b2c, ClinVar 20180605, ExAC V.1.0, CGW Version CGW\_V.613.

Manual somatic variant calling by molecular scientists and molecular pathologists will then be performed following interrogation of annotated variants using validated quality control metrics to distinguish somatic variants from population variants/SNPs and artefacts. All variants will be manually reviewed in Integrative Genome Viewer. Clinical interpretation of all DNA and RNA variants will be performed according to guidelines and standards for reporting somatic variant in cancer, in accordance with a joint consensus recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and the College of American Pathologists.<sup>21</sup> Somatic variants will be classified into a four tier system based on their clinical significance. Tier I, variants of strong clinical significance; tier II, variants of potential clinical significance; tier III variants of unknown clinical significance and tier IV, benign or likely benign variants. The results will be reviewed by a molecular tumour advisory panel (MTAP) (see section 3.2.2). The target turnaround time from receipt of tissue at the laboratory until delivery of a molecular pathology report is 4 weeks, chosen as an interval that will be clinically acceptable and logistically feasible.

**Molecular tumour advisory panel**

Molecular aberrations that result in a potentially actionable mutation will be reviewed by an MTAP, composed of at least one of each of the following experts: molecular pathologist, neuropathologist, medical oncologist, translational research scientist and bioinformatician. The MTAP will specifically refine the detailed molecular pathology results (typically in excess of 20 pages) into



a more concise 2-page format that provides: (1) expert recommendations regarding the clinical significance of each mutation specifically for brain tumours; (2) the availability of corresponding targeted drugs in Australia (either in trials or through other avenues); (3) prioritise treatments in the presence of multiple potential actionable mutations and (4) provide graded recommendations for potential therapies (see section 3.2.1). The MTAP report will be provided to the patient's treating physician, in addition to the usual detailed molecular pathology report generated by the reference laboratory, for their decision on the final course of treatment.

#### Disclosure of clinically significant information

All participants, including those with no actionable mutations, will be informed of the results of the MTAP by their treating physician. Molecular screening of tumours will predominantly generate information on somatic mutations in tumour tissue; however, germline pathogenic mutations may also be detected in such material. Participants will be asked to indicate whether they wish to receive information about hereditary cancer risk of potential importance to their health or that of their blood relatives. If potentially clinically significant

results are identified, the treating physician will refer the patient to an appropriate familial genetics clinic as per their institutional practices. No referral will be made if the participant has chosen not to be informed of clinically significant information pertaining to hereditary cancer risk.

#### Re-entry into study at progression

Patients treated with a targeted agent on study, who then progress while on study and are still appropriate for further surgery may have their most recent tumour submitted for re-evaluation with the same NGS panel. This will aim to provide preliminary data about the mechanism of resistance to the targeted agent used. Where relevant, a second MTAP report will be generated for this patient to guide the treating physician in selecting subsequent treatment.

#### Outcome measures

The outcomes measured in the LUMOS study are listed in [box 2](#).

Assessments will be performed according to the schedule shown in [table 4](#).

**Table 4** Schedule of assessments for LUMOS clinical trial, showing clinical, radiological and translational assessments

Molecular screening period	Follow-up period (time from the delivery of the MTAP report)				
	Screening and registration (presurgery or within 6 months postsurgery)	Delivery of molecular tumour advisory panel report	Follow-up (Q 8/52 recommended until PD on MRI)	At time of PD on MRI	End of follow-up
	Within 14 days prior to registration				2 years after registration
Informed consent	X				
Tissue for molecular screening	X			X (if clinically indicated)	
Clinic assessment <sup>8</sup>	X	X <sup>1</sup>	X	X	X
Blood tests: ▶ Haematology: FBC with differential ▶ Biochemistry: EUC, LFTs & glucose	X	X <sup>1</sup>	X	X	X
Brain MRI	X	X <sup>1</sup>	X	X	X
Assessment of dexamethasone use	X	X <sup>1</sup>	X	X	X
Blood for translational research	X	X <sup>1</sup>		X	X
Presurgery assessment	X				
Determination of treating physician <sup>6</sup>		X <sup>2</sup>			
Determination of current treatment			X	X	X
Rescreening for LUMOS				X	

Although recommended, all assessments performed after the delivery of the MTAP report are optional (1) Assessments do not need to be repeated if within 28 days of the delivery date of the MTAP report to the treating physician. (2) The treating physician is the physician who will be responsible for the administration of anticancer treatment to the patient where 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. EUC, Electrolytes, Urea and Creatinine; FBC, Full blood count; LFT, Liver function test; MTAP, molecular tumour advisory panel; PD, Progressive disease.



### Statistical design

For this pilot study, LUMOS will use a pragmatic sample size of 10 patients to evaluate the feasibility of this approach.

### Recruitment

Patients will be recruited from across five study sites within the 12-month period of the pilot study.

### Statistical analysis

The following variables will be described using standard summary statistics:

Patient recruitment:

- ▶ Number of eligible relapsed G2/3 glioma patients at each hospital site and the study overall.
- ▶ Number and percentage of screened relapsed G2/3 glioma patients enrolled.
- ▶ Demographic and clinical characteristics of enrolled patients.

Molecular screening metrics:

- ▶ Number and percentage of enrolled patients for whom tissue was successfully tested.
- ▶ Reasons for not undergoing molecular screening and for unsuccessful screening.
- ▶ Median time receipt of tissue by the reference laboratory to the time of receipt of MTAP report by the treating physician.
- ▶ In patients in whom a molecular screening report was received, the number of molecular targets identified that match drugs available through clinical trials of pharmaceutical access programmes.
- ▶ In patients in whom a target was identified, the proportion of patients who received targeted agents as a result of the MTAP recommendation.

### Patient and public involvement

The LUMOS pilot study concept was developed in response to the perceived unmet need for patients with recurrent lower grade glioma, due to the paucity of clinical trials in this space. Consumers are represented on the LUMOS trial management committee and are involved in decisions surrounding methods for communicating genomic information to patients in the study as well as suggestions for future studies. Information about the LUMOS study design will be promoted through patient support forums.

## ETHICS AND DISSEMINATION

### Research ethics approval

The LUMOS study was approved by the Human Research Ethics Committee (HREC) of (Royal Prince Alfred Hospital Zone) of the Sydney Local Health District. HREA (V.4, 20 November 2019), Protocol (V.1.2, 13 November 2019). Protocol No. X19-0383 and 2019/ETH12848. Other clinical sites provide oversight through local governance committees. Any substantial amendments to the study protocol will be reported to the HREC for approval

prior to implementation, and updated on the ANZCTR trial registry, with study investigators being advised in writing.

### DISCUSSION

To our knowledge, the LUMOS study is the first umbrella study for relapsed G2/3 glioma in adults. It is one of relatively few studies attempting to address the needs of this patient population and more importantly, providing a systematic way of testing numerous drugs for these patients. Multiple mutations exist in the tumours of these patients, some of which are arguably highly actionable such as Trk fusions,<sup>22</sup> but their low individual prevalence makes basket design or similar studies difficult to undertake. However, the main concern about such an approach has been the feasibility of successfully implementing such a trial in this patient population. LUMOS aims to address these concerns, working towards a pragmatic design for definitive testing of targeted agents for relapsed G2/3 gliomas in the future.

LUMOS will address key questions about technical feasibility and the speed of proposed screening techniques. One of the initial feasibility metrics we will investigate is the ability to obtain and use contemporaneous tissue for testing. A differentiating factor of LUMOS from other molecularly guided brain tumour studies is the use of contemporaneous tissue to guide treatment. Data from the GLASS consortium examining the evolution of mutations in low grade gliomas over time show that these occur in a stochastic fashion, resulting in the need for contemporaneous tissue to guide treatment decisions.<sup>13</sup> We will assess whether it is safe and feasible to obtain such tissue from patients at the time of relapse. We will also ascertain that the tissue thus obtained can be successfully evaluated using a common molecular panel, especially as tissue will need to be shipped to a reference laboratory. Lastly, the ability to provide a report in a clinically relevant time frame will also be tested. The aspirational turnaround time of 4 weeks in the LUMOS study (from the time of tissue receipt at the laboratory to delivery of the MTAP report) will be measured as a metric in this pilot study. In a previous analysis of 40 reported studies, the mean turnaround time including molecular screening and generation of a molecular pathology report was 38.4 days but the range was between 12.4 and 86 days; therefore, the aspirational target for LUMOS falls within these benchmarks,<sup>23</sup> despite some heterogeneity across studies regarding the definition of turnaround time.

We also plan to test the value of such an approach to the referring physician and their patients. While the concept of genomics-driven treatment recommendations is not new, there are still many challenges to implementing genomic information into routine cancer care. These challenges include interpretation of complex genomic information and limited availability of experts to provide such recommendations<sup>21</sup>. The LUMOS pilot study seeks to examine these challenges within the Australian context



by conducting molecular screening of patients from across several geographically dispersed institutions and examining the feasibility of such an approach in patients with relapsed G2/3 gliomas. We will also test the acceptability of succinct and tumour specific reporting with participating clinicians, hoping to overcome some of the known issues with interpretation of generic molecular pathology reports.<sup>24</sup> The MTAP was thus named to differentiate the neuro-oncology expertise provided by this panel from the tumour agnostic recommendations provided by the bioinformatics platform matching mutations to registered trials. The instances where these recommendations differ will be reported, thus illustrating the challenge of not only matching mutations to treatments but also ensuring avenues to access the treatments are communicated to treating physicians. We will also record any cases where study participation results in patients being treated with a targeted agent recommended by our testing and MTAP. However, this was not included as a formal study endpoint as we will not provide access to investigational drug, and the lack of access to such drugs for relapsed G2/3 patients currently makes this an unsuitable study endpoint. However, we fully anticipate that a successful feasibility trial would inform future such approaches.

Lastly, the LUMOS study has been designed to take advantage of the important opportunity to collect serial tissue in patients who have a second progression event during the study. Such tissue will undergo repeat molecular testing if their treating physician deems the participant appropriate for a further resection. This will serve two purposes; (1) affording the patient the potential to find another matched treatment at disease progression and (2) also contributing to our understanding of the molecular evolution of these tumours over time. While activation of genes associated with cell cycle, proliferation, invasion and tumour microenvironment are associated with progression of lower grade glioma to high grade glioma, serial tissue from patients to demonstrate this progression is lacking in clinical studies.<sup>25</sup>

In conclusion, LUMOS aims to establish the feasibility of a precision oncology, umbrella trial approach for this niche patient population with few established therapeutic opinions. Its success will be necessary to encourage future trials (whether from industry, academia or some combination thereof) to use a systematic approach that is arguably the only realistic way of testing drugs against a large but heterogeneous array of potentially actionable molecular targets in this patient population.

#### Author affiliations

<sup>1</sup>NHMRC Clinical Trials Centre, Camperdown, New South Wales, Australia

<sup>2</sup>Department of Medical Oncology, Royal North Shore Hospital, St Leonards, New South Wales, Australia

<sup>3</sup>Department of Medical Oncology, Chris O'Brien Lifehouse, Camperdown, New South Wales, Australia

<sup>4</sup>Kinghorn Cancer Centre, St Vincent's Hospital Sydney, Darlinghurst, New South Wales, Australia

<sup>5</sup>St Vincent's Clinical School, University of New South Wales, Darlinghurst, New South Wales, Australia

<sup>6</sup>Department of Medical Oncology, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia

<sup>7</sup>Medical School, The University of Western Australia, Perth, Western Australia, Australia

<sup>8</sup>School of Biomedical Sciences, Queensland University of Technology, Brisbane, Queensland, Australia

<sup>9</sup>Sid Faithfull Brain Cancer Laboratory, Cell and Molecular Biology Department, QIMR Berghofer, Herston, Queensland, Australia

<sup>10</sup>Department of Neuropathology, Brain and Mind Centre, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia

<sup>11</sup>The Jackson Laboratory for Genomic Medicine, Farmington, Connecticut, USA

<sup>12</sup>Oncogenic Signalling Laboratory, Telethon Kids Institute, Nedlands, Western Australia, Australia

<sup>13</sup>Department of Anatomical Pathology, PathWest Laboratory Medicine, Nedlands, Western Australia, Australia

<sup>14</sup>Faculty of Medicine, University of Queensland, Brisbane, Queensland, Australia

<sup>15</sup>Cancer Care Services, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia

<sup>16</sup>Department of Molecular Imaging and Therapy, Austin Health, Heidelberg, Victoria, Australia

<sup>17</sup>Olivia Newton-John Cancer Research Institute, Heidelberg, Victoria, Australia

<sup>18</sup>Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia

<sup>19</sup>School of Cancer Medicine, La Trobe University, Melbourne, Victoria, Australia

<sup>20</sup>Department of Neurosurgery, Royal North Shore Hospital, St Leonards, New South Wales, Australia

<sup>21</sup>Department of Neurosurgery, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia

<sup>22</sup>University of Queensland School of Medicine, Herston, Queensland, Australia

<sup>23</sup>Centre for Health Economics Research and Evaluation, University of Technology, Ultimo, New South Wales, Australia

<sup>24</sup>Department of Medical Oncology, Nelune Comprehensive Cancer Centre, Prince of Wales Hospital, Randwick, New South Wales, Australia

<sup>25</sup>Faculty of Medicine, University of New South Wales, Randwick, New South Wales, Australia

<sup>26</sup>Department of Neurology, Austin Health, Heidelberg, Victoria, Australia

<sup>27</sup>Department of Clinical Pharmacology, College of Medicine and Public Health, Flinders Medical Centre, Bedford Park, South Australia, Australia

<sup>28</sup>Department of Medical Oncology, Flinders Centre for Innovation in Cancer, Bedford Park, South Australia, Australia

<sup>29</sup>Preston Robert Tisch Brain Tumor Center at Duke, Department of Neurosurgery, Duke University Medical Center, Durham, North Carolina, USA

<sup>30</sup>Department of Radiation Oncology, Liverpool Cancer Therapy Centre, Liverpool, New South Wales, Australia

<sup>31</sup>Collaboration for Cancer Outcomes, Research and Evaluation, Ingham Institute for Applied Medical Research, Liverpool, New South Wales, Australia

<sup>32</sup>Department of Medical Oncology, Olivia Newton-John Cancer Centre at Austin Health, Heidelberg, Victoria, Australia

**Contributors** HG, BA, AKN, MEB, RV, AMS, RJ, RdAL, MK, TJ, EJB, BK, H-WS, SY, E-SK and EHB developed the study concept. BK, H-WS, CR, MAT and TG wrote drafts of the manuscript. AKN, SY, EHB, BWD, MEB, RV, TG, CR, MAT, TG, ZL, AMS, JP, RJ, RdAL, EJH, LMC, GK, MK, MH, ET, BA, E-SK and HG reviewed the manuscript and provided critical input.

**Funding** This work is supported by the Medical Research Future Fund through the Australian Brain Cancer Mission: Innovative Clinical Trials Grant (G203531). HG and AMS are supported by funding from the Victorian Government for the Centre for Research Excellence in Brain Tumours.

**Competing interests** None declared.

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

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is



properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iD

Benjamin Y Kong <http://orcid.org/0000-0001-8659-5591>

#### REFERENCES

- AIHW. *Brain and other central nervous system cancers*. Canberra, 2017.
- Surawicz TS, McCarthy BJ, Kupelian V, et al. Descriptive epidemiology of primary brain and CNS tumors: results from the central brain tumor registry of the United States, 1990-1994. *Neuro Oncol* 1999;1:14-25.
- Rigau V. Towards an intermediate grade in glioma classification. In: Duffau H, ed. *Diffuse low-grade gliomas in adults*. Springer, 2017: 101-8.
- Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro Oncol* 2021;23:1231-51.
- Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med* 2016;374:1344-55.
- van den Bent MJ, Brandes AA, Taphoorn MJB, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol* 2013;31:344-50.
- Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med Overseas Ed* 2005;352:987-96.
- Chinot OL, Honore S, Dufour H, et al. Safety and efficacy of temozolomide in patients with recurrent anaplastic oligodendrogliomas after standard radiotherapy and chemotherapy. *J Clin Oncol* 2001;19:2449-55.
- van den Bent MJ, Kros JM, Heimans JJ, et al. Response rate and prognostic factors of recurrent oligodendroglioma treated with procarbazine, CCNU, and vincristine chemotherapy. Dutch Neuro-Oncology group. *Neurology* 1998;51:1140-5.
- Reyes-Botero G, Laigle-Donadey F, Mokhtari K, et al. Temozolomide after radiotherapy in recurrent "low grade" diffuse brainstem glioma in adults. *J Neurooncol* 2014;120:581-6.
- Taal W, Dubbink HJ, Zonnenberg CBL, et al. First-line temozolomide chemotherapy in progressive low-grade astrocytomas after radiotherapy: molecular characteristics in relation to response. *Neuro Oncol* 2011;13:235-41.
- Whittle IR. The dilemma of low grade glioma. *J Neurol Neurosurg Psychiatry* 2004;75:ii31-6.
- Barthel FP, Johnson KC, Varn FS, et al. Longitudinal molecular trajectories of diffuse glioma in adults. *Nature* 2019;576:112-20.
- Uppstrom TJ, Singh R, Hadjigeorgiou GF, et al. Repeat surgery for recurrent low-grade gliomas should be standard of care. *Clin Neurol Neurosurg* 2016;151:18-23.
- Narang AK, Chaichana KL, Weingart JD, et al. Progressive low-grade glioma: assessment of prognostic importance of histologic reassessment and MRI findings. *World Neurosurg* 2017;99:751-7.
- Lasocki A, Gaillard F. Non-Contrast-Enhancing tumor: a new frontier in glioblastoma research. *AJNR Am J Neuroradiol* 2019;40:758-65.
- Cancer Genome Atlas Research Network, Brat DJ, Verhaak RGW, et al. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. *N Engl J Med* 2015;372:2481-98.
- Du T, Snedecor J, LoCoco JS. Abstract 565: analytical performance of TruSight® tumor 170 in the detection of gene fusions and splice variants using RNA from formalin-fixed, paraffin-embedded (FFPE) solid tumor samples. *Cancer Research* 2017;77:565.
- Chou D, Chen X, Purdy A, et al. Abstract 3732: analytical performance of TruSight® tumor 170 on small nucleotide variations and gene amplifications using DNA from formalin-fixed, paraffin-embedded (FFPE) solid tumor samples. *Cancer Research* 2017;77:3732.
- LoCoco JS, Teng L, Chou D, et al. Abstract 5354: evaluation of quantity, quality and performance with the TruSight® tumor 170 solid tumor profiling assay of nucleic acids extracted from formalin-fixed paraffin-embedded (FFPE) tissue sections. *Cancer Research* 2017;77:5354.
- van de Haar J, Hoes L, Voest E. Advancing molecular tumour boards: highly needed to maximise the impact of precision medicine. *ESMO Open* 2019;4:e000516.
- Wang Y, Long P, Wang Y, et al. NTRK fusions and TRK inhibitors: potential targeted therapies for adult glioblastoma. *Front Oncol* 2020;10:593578.
- Luchini C, Lawlor RT, Milella M, et al. Molecular tumor boards in clinical practice. *Trends Cancer* 2020;6:738-44.
- Gray SW, Hicks-Courant K, Cronin A, et al. Physicians' attitudes about multiplex tumor genomic testing. *J Clin Oncol* 2014;32:1317-23.
- Ceccarelli M, Barthel FP, Malta TM, et al. Molecular profiling reveals biologically discrete subsets and pathways of progression in diffuse glioma. *Cell* 2016;164:550-63.
- Picca A, Berzero G, Sanson M. Current therapeutic approaches to diffuse grade II and III gliomas. *Ther Adv Neurol Disord* 2018;11:1756285617752039.
- Pignatti F, van den Bent M, Curran D, et al. Prognostic factors for survival in adult patients with cerebral low-grade glioma. *J Clin Oncol* 2002;20:2076-84.
- Tesileanu CMS, Dirven L, Wijnenga MMJ, et al. Survival of diffuse astrocytic glioma, IDH1/2 wildtype, with molecular features of glioblastoma, WHO grade IV: a confirmation of the cIMPACT-NOW criteria. *Neuro Oncol* 2020;22:515-23.
- Reyes-Botero G, Laigle-Donadey F, Mokhtari K, et al. Temozolomide after radiotherapy in recurrent "low grade" diffuse brainstem glioma in adults. *J Neurooncol* 2014;120:581-6.
- Chamberlain MC, Kormanik P. Salvage chemotherapy with taxol for recurrent anaplastic astrocytomas. *J Neurooncol* 1999;43:71-8.
- Chamberlain MC, Wei-Tsao DD, Blumenthal DT, et al. Salvage chemotherapy with CPT-11 for recurrent temozolomide-refractory anaplastic astrocytoma. *Cancer* 2008;112:2038-45.
- Chamberlain MC, Tsao-Wei DD, Groshen S. Salvage chemotherapy with cyclophosphamide for recurrent temozolomide-refractory anaplastic astrocytoma. *Cancer* 2006;106:172-9.
- Pace A, Vidiri A, Galiè E, et al. Temozolomide chemotherapy for progressive low-grade glioma: clinical benefits and radiological response. *Ann Oncol* 2003;14:1722-6.
- Desjardins A, Quinn JA, Vredenburgh JJ, et al. Phase II study of imatinib mesylate and hydroxyurea for recurrent grade III malignant gliomas. *J Neurooncol* 2007;83:53-60.
- Duerinck J, Du Four S, Sander W, et al. Sunitinib malate plus lomustine for patients with Temozolomide-refractory recurrent anaplastic or low-grade glioma. *Anticancer Res* 2015;35:5551-7.
- Reardon DA, Desjardins A, Vredenburgh JJ, et al. Phase II study of Gleevec plus hydroxyurea in adults with progressive or recurrent low-grade glioma. *Cancer* 2012;118:4759-67.
- Kesavabhotla K, Schlaff CD, Shin B, et al. Phase I/II study of oral erlotinib for treatment of relapsed/refractory glioblastoma multiforme and anaplastic astrocytoma. *J Exp Ther Oncol* 2012;10:71-81.
- Kreisl TN, Zhang W, Oda Y, et al. A phase II trial of single-agent bevacizumab in patients with recurrent anaplastic glioma. *Neuro Oncol* 2011;13:1143-50.
- Chamberlain MC, Johnston S. Salvage chemotherapy with bevacizumab for recurrent alkylator-refractory anaplastic astrocytoma. *J Neurooncol* 2009;91:359-67.
- Kim Y-H, Nonoguchi N, Paulus W, et al. Frequent BRAF gain in low-grade diffuse gliomas with 1p/19q loss. *Brain Pathol* 2012;22:834-40.
- Dubbink HJ, Atmodimedjo PN, Kros JM, et al. Molecular classification of anaplastic oligodendroglioma using next-generation sequencing: a report of the prospective randomized EORTC brain tumor group 26951 phase III trial. *Neuro Oncol* 2016;18:388-400.
- Behling F, Barrantes-Freer A, Skardelly M, et al. Frequency of BRAF V600E mutations in 969 central nervous system neoplasms. *Diagn Pathol* 2016;11:55.
- Stransky N, Cerami E, Schalm S, et al. The landscape of kinase fusions in cancer. *Nat Commun* 2014;5:4846.