

# Cancer Research Wales Brain Tumour Conference



19th September 2025



Sophia Gardens Cricket Ground

## Manipulating T-cell immune responses to improve anti-Glioblastoma immunity

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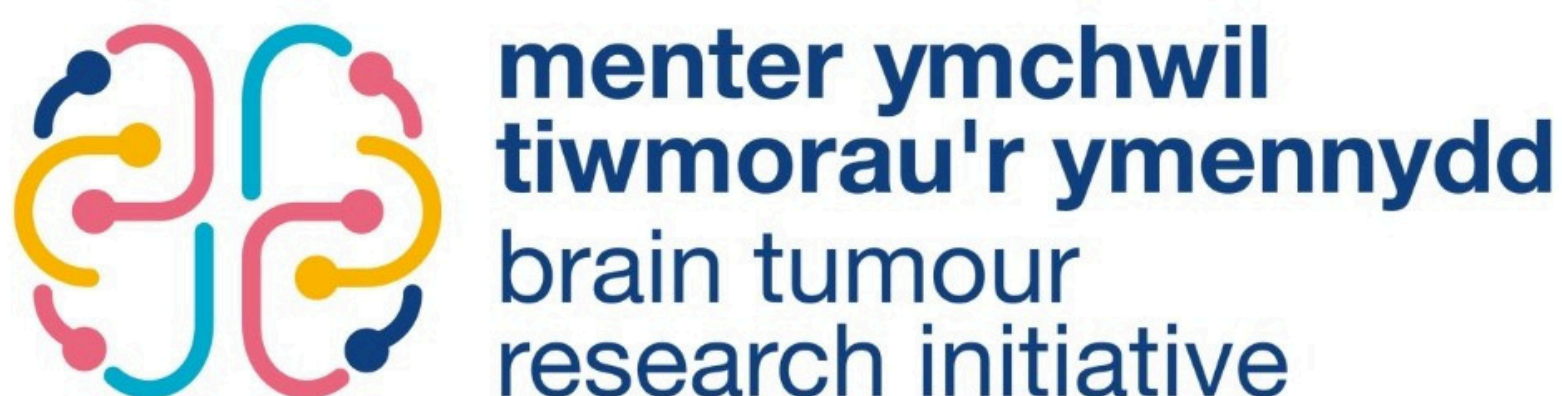
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Glioblastoma (GBM) is the most aggressive and malignant primary brain tumour. There are limited treatment options including surgery, radiotherapy, and temozolomide chemotherapy, but these usually provide temporary relief with tumour return inevitable. Even with aggressive treatment GBM is fatal with a median survival of ~15 months and a five-year survival rate of 6.9%. This highlights the urgent need for novel treatments.

Current therapeutic approaches for GBM largely fail to prevent relapse due to genetic and cellular heterogeneity within the tumour. Whilst the use of immune checkpoint blockade (ICB) or chimeric antigen receptor T-cells (CAR-T-cells) have been trialled as immune-modulators in GBM, both have failed to provide any improved tumour control indicating that other targets are needed. This may be due to other immunosuppressive mechanisms in the tumour microenvironment (TME) and/or due to sub-optimal priming of GBM-specific T-cells. Overcoming immunosuppression in the TME is therefore vital for the success of immunotherapies targeting GBM moving forward.

The immune-modulating cytokine IL-10 plays a major role in promoting an immune-suppressive TME and has been shown to promote GBM tumour progression. CD4<sup>+</sup> T-cells are known to release IL-10 (T<sub>H</sub>1, T<sub>H</sub>2 and Regulatory T-cells) during inflammation, however, how CD4<sup>+</sup> T-cell mediated IL-10 release contributes to GBM progression remains unknown.

My preliminary results show that IL-10 is over-produced in a mouse model of GBM and that blocking IL-10 signalling gives rise to a reduction in tumour burden, greater survival and an increase in activated immune cells in the brain. These data imply that targeted blockade of IL-10 signalling could provide a useful treatment option to improve GBM outcome in humans.





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## Advanced MRI techniques highlight distinct vascular characteristic across Glioma subtypes

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### Introduction

Gliomas generate an extra blood supply to meet their growing need for nutrients and oxygen, altering normal physiology and tissue metabolism. The need of proliferating cells for extra blood supply changes the structure and function of the brain's normal vasculature. Vascular proliferation is a pathological hallmark of gliomas, resulting in abnormal and dysfunctional vessels.

### Aim

In this project, we used advanced MRI techniques to detect different vascular characteristics in glioma subtypes.

### Methods

We acquired MRI quantitative susceptibility maps (QSM) from 27 patients (mean age  $45.5 \pm 8.8$  years; 20M) diagnosed with glioma. Vascular parameters, including vessel density, vascular diameter, and oxygen extraction fraction, were extracted from the QSM maps.

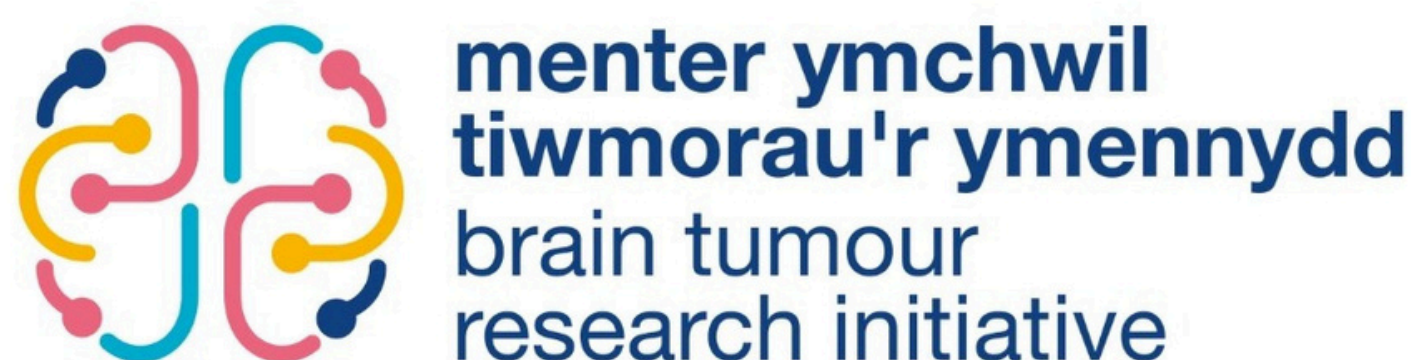
The group was divided according to tumour diagnosis (Astrocytoma, Glioblastoma, Oligodendroglioma) and WHO grade (low vs. high) to examine vascular differences among tumour subtypes and grades.

### Results

We observed distinct metabolic and vascular characteristics across glioma subtypes (diagnosis and grade), consistent with existing knowledge that more aggressive brain tumours develop their own blood supply, leading to alterations in vascular parameters.

### Conclusion

Our findings highlight the potential of QSM maps to identify subtype-specific vascular features. Integrating QSM mapping into routine clinical assessments in gliomas could support tumour diagnosis and characterization.





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## UK radiotherapy practice for Oligodendroglioma – data from the APPROACH trial (ISRCTN:1339049) radiotherapy quality assurance (RTQA) programme

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### Aims

A comprehensive RTQA programme for the APPROACH trial (Analysis of Proton vs Photon Radiotherapy in Oligodendroglioma and Assessments of Cognitive Health) includes a pre-accrual facility questionnaire. Information on equipment, software, planning and outlining techniques was captured to assess variations in practice for UK centres enrolled in the trial.

### Methods

Between December 2022 to November 2024 the national Radiotherapy Trials Quality Assurance (RTTQA) Group circulated a questionnaire to 21 photon and 2 proton centres. Data from 21 photon centres is presented here.

### Results

Each centre routinely uses thermoplastic shells for immobilisation and acquires CT planning scans with 1-3mm slice thickness. Some centres co-register the post-operative MRI, whilst others acquire dedicated planning MRI scans. MRI slice thickness ranges from 0.8-3mm. T1+ contrast and T2/FLAIR MRI sequences are co-registered.

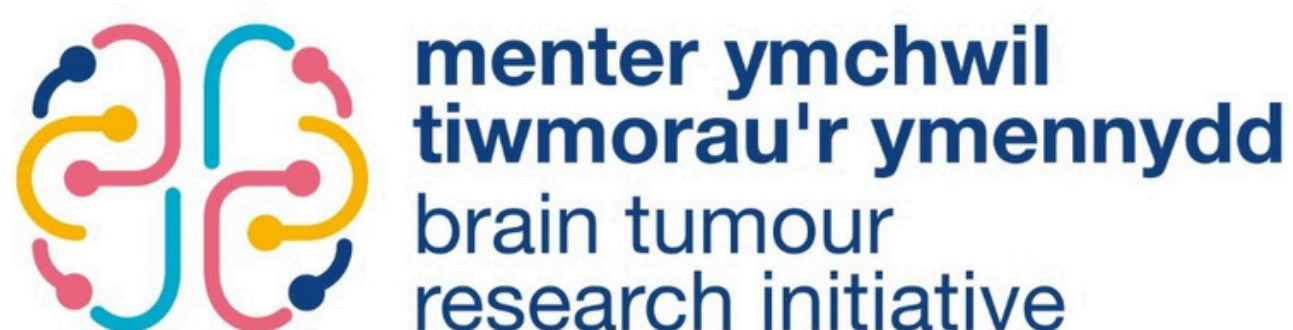
All 21 centres routinely use CTV margins of 10-15mm, PTV margins of 3-5mm and radiotherapy doses consistent with the APPROACH trial protocol. All centres use Volumetric Arc Therapy (VMAT).

All centres routinely contour brainstem, chiasm, optic nerve and eyes, with 95% (20/21) also contouring lens and spinal cord. Cochleas were contoured by 81% (17/21). There is variability between centres in the frequency of lacrimal gland, pituitary, optic tracts, brain, retina, cornea and parotid contouring. Hippocampi are routinely contoured by 19% (4/21). No centres routinely contour the hypothalamus.

Auto-contouring for organs-at-risk (OARs) is used by 62% of centres (13/21) and in 52% of centres OARs may be contoured by a multi-professional team member.

### Conclusion

The FQ data highlights a consistent approach to immobilisation, volume expansion, dose and fractionation using VMAT delivery with variation between centres in pre-treatment imaging processes and OAR contouring. The APPROACH trial aims to improve consistency in practice for oligodendroglioma in the UK, to standardise the use of a dedicated planning MRI and thin slice image acquisition, and introduce hippocampal and hypothalamus contouring.





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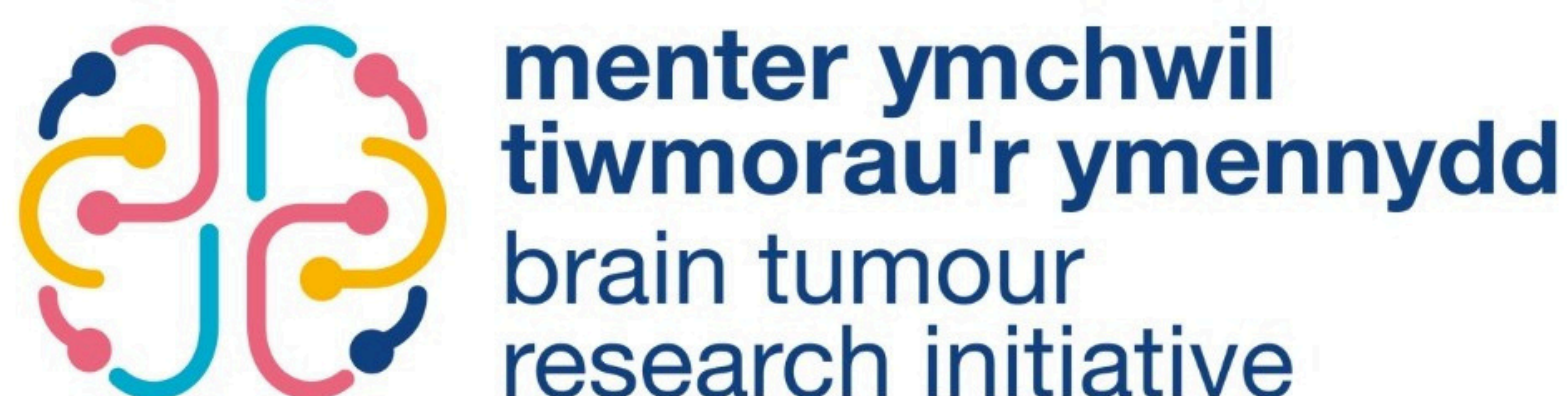
## Targeting glioblastoma with precision adenoviral therapies

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<sup>1</sup>*Division of Cancer and Genetics, School of Medicine, Cardiff University, Heath Park, Cardiff, CF14 4XN, UK.*

Glioblastoma (GBM) is a devastating form of brain cancer with poor survival rates and a significant unmet clinical need. Existing virotherapies lack the required selectivity and power to be effective in GBM. Adenoviruses (Ad) are popular vectors for a range of clinical applications. Species C, Ad5, is well documented experimentally, but its utility is limited by high prevalence of pre-existing immunity and significant “off-target” interactions which negatively affect dose limiting toxicities. Our lab has developed the Ad5<sub>NULL</sub> platform with adverse interactions ablated. Vectors derived from adenovirus species with lower rates of pre-existing immunity are also beneficial for clinical applications. We have engineered an alternative vector based on the low seroprevalence species D, Ad10. Therefore, we have two established vectors primed for tumour selective targeting.

We developed Ad5<sub>NULL</sub>-RGD and Ad10-RGD vectors which efficiently and selectively target  $\alpha\beta3/5$  integrins, upregulated in GBM, improving ‘on tumour’ activity and limiting detrimental off target effects. Our data indicates Ad5<sub>NULL</sub>-RGD demonstrates an improvement in transduction compared to Ad5 and Ad5-RGD. We show selective transduction in GBM cell lines and glioma stem cells (GSCs) demonstrating Ad5<sub>NULL</sub>-RGD that is well suited to GBM applications. Additionally, we demonstrate that Ad10-RGD efficiently transduces  $\alpha\beta3$  positive GSCs. We have evaluated these vectors in relevant models of GBM including brain organoids and patient-derived 3D cultures. We aim to develop these vectors further by incorporating transgenes that mediate tumour-specific replication and cell killing. These novel precision virotherapies hold potential as new therapeutic options for devastating brain cancers of significant unmet clinical need.





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## **Developing a Core Patient-Focused Outcome Set to Support Care in Glioma: A Study Protocol for the COMBaT Study.**

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### **Aims**

Gliomas account for around 80% of malignant primary brain tumours and are associated with an unpredictable clinical trajectory. People living with glioma experience varying, complex and often unmet care needs. Regularly identifying outcomes that matter most to patients could improve symptom management, treatment provision and quality of life. However, the evidence highlights a lack of consistent and structured approaches to assess these needs in clinical settings. The COMBaT study aims to develop a core set of patient-focused outcomes that reflect the needs of people living with glioma and determine a pathway to collect these data in NHS settings, with a focus on services in Wales.

### **Methods**

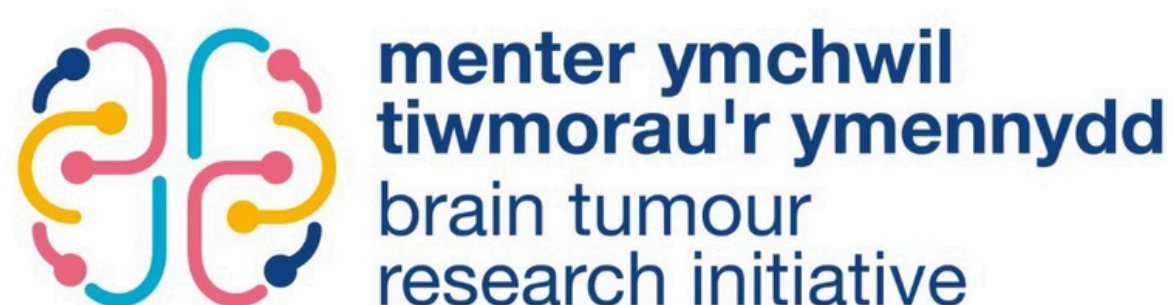
COMBaT is a mixed-methods, multistage study. We are currently reviewing the qualitative evidence base, including an updated systematic review and qualitative synthesis of outcomes used in clinical settings, alongside a secondary analysis of 19 interviews with people living with glioma. A preliminary list of outcomes will be drafted and refined through a two-rounds modified Delphi process to achieve consensus on the prioritisation of the outcomes with key stakeholders. These stakeholders will include people living with glioma, healthcare professionals and members of NHS services (including governance and data experts). The psychometric properties of patient-reported outcome measures identified by participants will be reviewed and mapped to the prioritised outcomes. A final stakeholder workshop will co-develop an implementation strategy for collecting core outcomes in NHS settings, particularly in Wales.

### **Results**

This study is in its initial stages and is expected to conclude in January 2027. Anticipated outputs include a core outcome set and measures for glioma and an implementation strategy to collect these outcomes in clinical practice within NHS data capture systems.

### **Conclusion**

Defining core patient-focused outcomes is essential for meaningful routine assessment to achieve patient-centred care and inform future service development across NHS care pathways.





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## Investigating the role of FGFR3 expression in Glioblastoma stem cells, using an in vitro culture system for cellular quiescence

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<sup>1</sup>European Cancer Stem Cell Research Institute, School of Biosciences, Cardiff University

### **Aims:**

Glioblastoma (GBM) exhibits significant cellular heterogeneity, contributing to its aggressiveness and therapy resistance. Glioblastoma stem cells (GSCs) are a key component of this heterogeneity and can adopt quiescent states, which may underlie treatment resistance and tumour recurrence. This study aims to establish a reversible in vitro system to model quiescence in GSCs. Using this model, we investigate the role of FGFR3 in regulating the quiescent state, assess its association with slow-dividing populations, and determine whether FGFR3 is required for the induction or maintenance of quiescence. This approach aims to better understand mechanisms driving phenotypic plasticity in GBM.

### **Methods:**

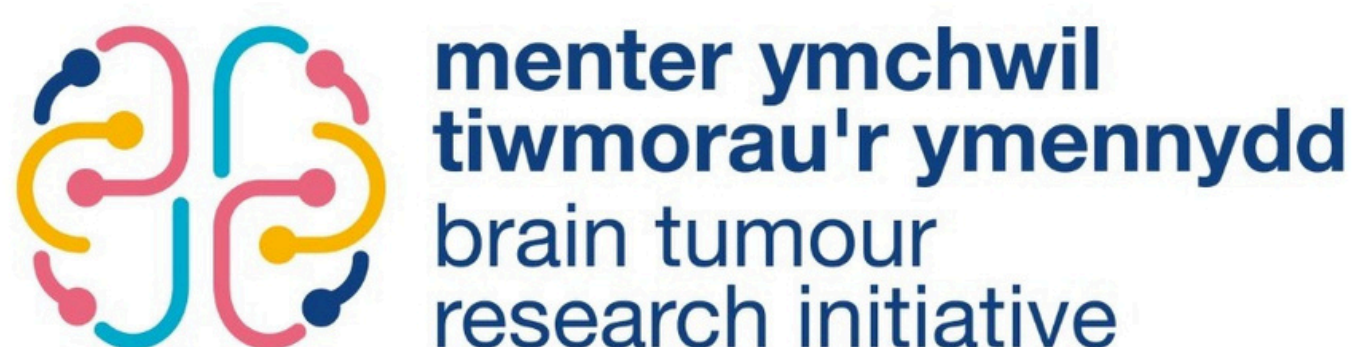
We employed a reversible in vitro culture system to induce GSC quiescence via BMP4 stimulation and reactivation through growth factor reintroduction. Proliferation and quiescence were assessed by immunofluorescence and western blotting for key markers. FGFR1 and FGFR3 expression were analysed using flow cytometry, and CFSE dye-tracking assays identified slow-dividing populations. FGFR1 and FGFR3 positive cells were isolated by FACS and assessed in primary and secondary sphere formation assays. FGFR3 function was interrogated via shRNA-mediated knockdown.

### **Results:**

FGFR3 was significantly upregulated under BMP4-induced quiescent conditions, while FGFR1 was enriched in proliferative cultures. Flow cytometry confirmed reciprocal receptor expression. CFSE analysis revealed FGFR3 cells were enriched in slowly dividing populations. FGFR3 positive cells formed few primary spheres but showed enhanced secondary sphere capacity, consistent with a slow-cycling, stem-like phenotype. FGFR3 knockdown impaired GSCs ability to enter quiescence, as cells retained high proliferation and failed to upregulate quiescence markers.

### **Conclusions:**

FGFR3 is a novel regulator of GSC quiescence, marking a slow-dividing subpopulation essential for dormancy. These findings highlight FGFR3 as a potential therapeutic target to eliminate quiescent treatment-resistant cells that drive GBM recurrence and treatment failure.





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## Hippocampal Dosimetry and Neurocognitive Function in Patients undergoing Stereotactic Radiosurgery.

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<sup>1</sup>Velindre University NHS Trust, Clinical Oncology, Cardiff. <sup>2</sup>Cardiff University, School of Medicine. <sup>3</sup>Cwm Taf University Health Board, Clinical Psychology <sup>4</sup>University of Bath, Clinical Psychology <sup>5</sup>Velindre University NHS Trust, Medical Physics

### **Aims:**

Despite the precision of stereotactic radiosurgery (SRS) up to 60% of patients develop NCF impairment(1). The hippocampus is implicated in NCF impairment, however, there is no dose tolerance defined for SRS. This prospective observational study aims to correlate NCF changes with hippocampal dosimetry.

### **Methods:**

Patients underwent NCF testing and quality of life (QoL) measure at baseline, 1,3, and 6-months following SRS. NCF tests included Hopkins learning verbal test – revised (HVLT-TR), trail making test, controlled oral word association test and digit span. QoL was measured using the European organisation for research and treatment of cancer core quality of life questionnaire (EORTC QLQ-C30) questionnaires at each time point. The radiation therapy oncology group protocol was utilised to delineate hippocampal volumes (5). Fisher-exact-test was performed to test statistical significance. Multivariate analysis was performed for confounding factors.

### **Results:**

36 patients were recruited. Mean age was 64 years and median WHO performance status was 1. Participants who demonstrated a decline in HVLT-TR tests score at 1-month had a mean dose to 0.1cc of the hippocampus of 5.39Gy compared to 2.28Gy in participants who had maintained HVLT-TR T-score, (p-value=0.026). This difference was not detected at the 3-or 6-months. This finding was irrespective of whole brain V12Gy, V5Gy and D10cc doses. The global QoL scores were reduced in the patients with reduced HVLT-TR T-score vs those with retained score: 67.36(95%CI 61.99–72.73) vs 57.41,(95%CI 54.17–60.65) respectively.

### **Conclusion:**

Higher hippocampal dose is associated with acute NCF impairment. This has a significant impact on QoL in these patients. By reducing the dose to the hippocampus during treatment planning, it may be possible to prevent acute deterioration in NCF and improve patient's QoL. Contouring the hippocampus as an organ at risk during SRS treatment planning and prioritising it as an optimal but not a mandatory constraint should be considered.





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## **Telomere dysfunction and fusions in glioblastoma - defining prognosis and genome instability**

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\*Joint senior authors

### **Background**

Glioblastoma (GBM) remains a cancer of unmet need. Identifying biomarkers for patient stratification and prediction of response to therapy is a priority. Telomeres protect chromosome-ends from aberrant DNA damage responses (DDR), and telomere attrition has been shown to drive genome instability and clonal evolution in several cancers. We examined the relationship between telomere dysfunction, fusion and clinical outcome in GBM patients.

### **Methods**

146 adults with molecular GBMs had tumour TL assessed with high-throughput single telomere length analysis. Assays for extrachromosomal c-circles and TERT promoter mutation status were performed, to assess underlying telomere maintenance mechanisms. Uni- and multi-variable analysis was conducted to assess tumour TL impact on OS and PFS. Single-molecule PCR coupled with long-read nanopore sequencing was used to characterise telomere fusions.

### **Results**

GBMs displayed shortened telomeres (median TL 4.0kb), unrelated to age at diagnosis or MGMT methylation status. Short TL was negatively predictive for OS on multivariable analysis (HR 4.81, p=0.009), this was more pronounced in patients with complete resection at index surgery (HR 21.55, p=0.0074). Widespread telomere fusions were observed that revealed microhomology, subtelomeric deletions and insertions of genomic loci within complex chromosomal rearrangements. Insertions often included protein-coding genes with driver mutations, long non-coding RNA, telomeric repeats, and subtelomeric and pericentromeric regions. This mutational spectrum suggested utilisation of specific DNA repair pathways in mediating telomere fusion.

### **Conclusion**

This study provides mechanistic evidence of dysfunctional telomeres in GBMs, with high resolution TL analysis together with MGMT methylation status providing powerful independent prognostic information. The data defines patient subgroups (MGMT unmethylated, short TL) which may benefit from alternatives to TMZ, and aberrant DDR signatures could help inform stratification within adaptive platform trials of DDR inhibitors.

