



UNIVERSITY OF
PLYMOUTH

Peninsula Medical School
Faculty of Health



2024-04-11

Adult brain tumour research in 2024: Status, challenges and recommendations

Lucy F. Stead *University of Leeds*

Karin Purshouse *University of Edinburgh*

Helen J. Bulbeck *Brainstrust*

Alasdair G. Rooney *University of Edinburgh*

Karen E. Noble *Brain Tumour Research*

et al. *See next page for additional authors*

Let us know how access to this document benefits you

General rights

All content in PEARL is protected by copyright law. Author manuscripts are made available in accordance with publisher policies. Please cite only the published version using the details provided on the item record or document. In the absence of an open licence (e.g. Creative Commons), permissions for further reuse of content should be sought from the publisher or author.

Take down policy

If you believe that this document breaches copyright please [contact the library](#) providing details, and we will remove access to the work immediately and investigate your claim.

Follow this and additional works at: <https://pearl.plymouth.ac.uk/pms-research>

Recommended Citation

Stead, L., Purshouse, K., Bulbeck, H., Rooney, A., Noble, K., Carruthers, R., Thompson, G., Hamerlik, P., Yap, C., Kurian, K., Jefferies, S., Lopez, J., Jenkinson, M., & Hanemann, C. (2024) 'Adult brain tumour research in 2024: Status, challenges and recommendations', *Neuropathology and Applied Neurobiology*, 50(2).

Available at: <https://doi.org/10.1111/nan.12979>

This Article is brought to you for free and open access by the Faculty of Health at PEARL. It has been accepted for inclusion in Peninsula Medical School by an authorized administrator of PEARL. For more information, please contact openresearch@plymouth.ac.uk.

Authors

Lucy F. Stead, Karin Purshouse, Helen J. Bulbeck, Alasdair G. Rooney, Karen E. Noble, Ross D. Carruthers, Gerard Thompson, Petra Hamerlik, Christina Yap, Kathreena M. Kurian, Sarah J. Jefferies, Juanita S. Lopez, Michael D. Jenkinson, and C. Oliver Hanemann



UNIVERSITY OF
PLYMOUTH

PEARL

Adult brain tumour research in 2024

Purshouse, Karin; Bulbeck, Helen J.; Rooney, Alasdair G.; Noble, Karen E.; Carruthers, Ross D.; Thompson, Gerard; Hamerlik, Petra; Yap, Christina; Kurian, Kathreena M.; Jefferies, Sarah J.; Lopez, Juanita S.; Jenkinson, Michael D.; Hanemann, C. Oliver; Stead, Lucy F.

Published in:

Neuropathology and Applied Neurobiology

DOI:

[10.1111/nan.12979](https://doi.org/10.1111/nan.12979)

Publication date:

2024

Document version:

Peer reviewed version

Link:

[Link to publication in PEARL](#)

Citation for published version (APA):

Purshouse, K., Bulbeck, H. J., Rooney, A. G., Noble, K. E., Carruthers, R. D., Thompson, G., Hamerlik, P., Yap, C., Kurian, K. M., Jefferies, S. J., Lopez, J. S., Jenkinson, M. D., Hanemann, C. O., & Stead, L. F. (2024). Adult brain tumour research in 2024: Status, challenges and recommendations. *Neuropathology and Applied Neurobiology*, 50(2), Article e12979. <https://doi.org/10.1111/nan.12979>

All content in PEARL is protected by copyright law. Author manuscripts are made available in accordance with publisher policies. Wherever possible please cite the published version using the details provided on the item record or document. In the absence of an open licence (e.g. Creative Commons), permissions for further reuse of content should be sought from the publisher or author.

Download date: 28. Oct. 2024

Adult Brain Tumour Research in 2024: Status, Challenges and Recommendations

Karin Purshouse¹, Helen J Bulbeck², Alasdair G Rooney³, Karen E Noble⁴, Ross D Carruthers⁵, Gerard Thompson^{3,6}, Petra Hamerlik⁷, Christina Yap⁸, Kathreena M Kurian⁹, Sarah J Jefferies¹⁰, Juanita S Lopez¹¹, Michael D Jenkinson¹², C Oliver Hanemann¹³, Lucy F Stead¹⁴

¹ Institute of Genetics and Cancer, The University of Edinburgh, Crewe Road, Edinburgh, EH4 2XU

² brainstrust, 4 Yvery Court, Castle Road, Cowes PO31 7QG

³ Centre for Clinical Brain Sciences, The University of Edinburgh, Chancellor's Building, 49 Little France Crescent, Edinburgh EH16 4SB.

⁴ Brain Tumour Research, Suite 37, Shenley Pavilions, Chalkdell Drive, Shenley Wood, Milton Keynes MK5 6LB

⁵ Beatson West of Scotland Cancer Centre, 1053 Great Western Road, Glasgow G12 0YN

⁶ Department of Clinical Neurosciences, NHS Lothian, 50 Little France Crescent, Edinburgh EH16 4SA

⁷ Division of Cancer Sciences, University of Manchester, 555 Wilmslow Rd, Manchester, M20 4GJ

⁸ Clinical Trials and Statistics Unit, 15 Cotswold Road, Sutton, SM2 5NG

⁹ Bristol Brain Tumour Research Centre, Bristol Medical School, University of Bristol BS8 1UD

¹⁰ Oncology Department, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ

¹¹ Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, Sutton SM2 5PT

¹² University of Liverpool & Walton Centre, Lower Lane, Liverpool, L9 7LJ

¹³ Peninsula Medical School, University of Plymouth, John Bull Building, Research Way, Plymouth PL6 8BU

¹⁴ Leeds Institute of Medical Research, University of Leeds, Leeds, UK, LS9 7TF

Conflicts of interest: GT has provided consultation for QMENTA and Optum Health. PH is a part-time employee at AstraZeneca. SJJ has a private practice and has investments in Genesis Cancer Centre, Newmarket. JSL has received research funding from Roche-Genentech, Astex, and Basilea, and is a member of the Scientific Advisory Boards for Roche-Genentech, Basilea, Eisai, GSK, and Pierre-Faber. MDJ has received Honoraria from BrainLab, Integra, Servier and GSK. COH received research funding from BergenBio. LFS is a member of the Scientific Advisory Board for CoSyne Therapeutics Ltd.

Funding: Cancer Research UK to RDC. The Brain Tumour charity to PH. Sir John Fisher Foundation and Royal College of Surgeons of England to MDJ. Brain Tumour Research to COH. UKRI Future Leaders Fellowship [MR/T020504/1] to LFS.

Abstract

In 2015, a groundswell of brain tumour patient, carer and charity activism compelled the UK Minister for Life Sciences to form a brain tumour research task and finish group. This resulted, in 2018, with the UK government pledging £20m of funding, to be paralleled with £25m from Cancer Research UK, specifically for neuro-oncology research over the subsequent 5 years. Herein, we review if and how the adult brain tumour research landscape in the UK has changed over that time, and what challenges and bottlenecks remain. We have identified seven universal brain tumour research priorities, and three cross-cutting themes, which span the research spectrum from bench to bedside and back again. We discuss the status, challenges, and recommendations for each one, specific to the UK.

Key Points

- Brain cancer leads to more years of life-loss, per patient than any other cancer, but brain tumour research has, historically, been underfunded in the UK;
- An increase in UK public awareness of brain cancer prompted the government, and leading UK cancer charity, to pledge a cumulative £45m of funding for neuro-oncology research in 2018;
- Herein, a group of multi-disciplinary brain cancer experts assimilate information from cross-sector focus groups and commissioned reports to provide current perspectives on the adult neuro-oncology research landscape in the UK;
- This position paper includes UK-specific recommendations for addressing the significant challenges and bottlenecks that remain for adult brain tumour research.

Brain cancer is considered to be a rare disease, but it leads to more years of life loss per patient than any other cancer, and UK incidence rates are on the rise¹. The trauma and tragedy that so often surrounds a brain cancer diagnosis led to an increase in UK public awareness, as distressing stories in which young families, or high-profile personalities, were devastatingly affected became more widespread. UK parliament was petitioned to fund more research into brain tumours in 2015, triggering a debate in the House of Commons in 2016. A task and finish group was established, which highlighted several scientific, clinical, economic and societal challenges that are specific to brain cancer and have contributed to the fact that cure rates have remained low for decades. For example, the median survival of the most common aggressive primary brain tumour, glioblastoma, is 12-18 months, with 25% surviving >1 year and 5% surviving >5 years¹ and this has not improved in over 20 years². In 2018, based on the suggestions of the task and finish group, the UK government made a pledge to commit £20m to fund brain tumour research, paralleled with a Cancer Research UK (CRUK) commitment of £25m, ring-fenced for neuro-oncology research over the subsequent 5 years.

In 2021, the UK National Cancer Research Institute (NCRI) Brain Group (a multi-disciplinary community of researchers and consumers focused on clinical and translational aspects specific to brain tumours) held four focus-group-like sessions, attracting >60 participants representing all neuro-oncology disciplines and sectors, to discuss how the brain tumour research landscape had changed in the UK since that pledge. The aim was to garner current perspectives on UK neuro-oncology research and to highlight persistent or new bottlenecks and opportunities. Whilst the NCRI ceased to exist at the end of 2023, the established working group persevered, assimilating the information received from the NCRI sessions with that from additional panels convened, or reports published, by Cancer Research UK (CRUK) in 2019³, the National Institute of Health Care and Research (NIHR)-funded James Lind Alliance in 2015⁴, and the UK All-Party Parliamentary Group on Brain Tumours (APPGBT) in early 2023⁵. This assimilation of fact, experience and opinion from across the whole community resulted in the identification of **seven research priorities (Fig.1)** that are common to brain cancer research globally and that span the full research pipeline and patient journey:

1. Prompter diagnosis;
2. Identify target drivers of malignancy;
3. Using suitable preclinical models and assays;
4. Provide sufficient evidence for therapeutic opportunity;
5. Develop accessible, innovative, and evidence-based clinical trials;
6. Treat every patient as a research patient;
7. Facilitate living beyond a brain tumour.

Herein we discuss these priorities specifically in terms of the status, challenges, and recommendations for the UK. Pertinent to all are **three cross-cutting themes**: collaborative networks and initiatives, funding, and training (**Fig. 1**). Again, these are discussed with regard to the UK landscape. Biological and clinical pathways are distinct for paediatric and adult brain tumours, making their investigation and clinical management quite disparate. For that reason, this position paper focuses on adult disease.

Several initiatives and epidemiological studies have attempted to compare adult (neuro)oncology metrics worldwide⁶⁻⁹. To illustrate how the UK fares against other brain cancer research active countries, we have extracted some key statistics, where they were available from published research or databases (**Fig. 2**). This indicates that the UK has low relative survival across numerous brain cancers^{6,8} (**Fig. 2A**). Estimates of incidence and mortality rates for brain tumours are similar for the UK (**Fig. 2B**), though comparing these metrics are difficult owing to the different ways in which it is recorded and collected worldwide⁹. However, the data does highlight that the UK has relatively fewer clinical trials compared with these other countries⁷ (**Fig. 2C**). The aim of this position paper is to encourage UK funders, academia, industry and the National Health Service (NHS) to rally behind the identified priorities and focus their efforts on releasing some of the recognised bottlenecks to expedite more effective brain tumour research to maximise patient benefit. To facilitate this, we have employed a scoring system for our recommendations to say whether we believe each one is short-term and easily achievable (SE), intermediate-term and moderately difficult to achieve (IM) or long-term, ambitious and difficult to achieve (LD).

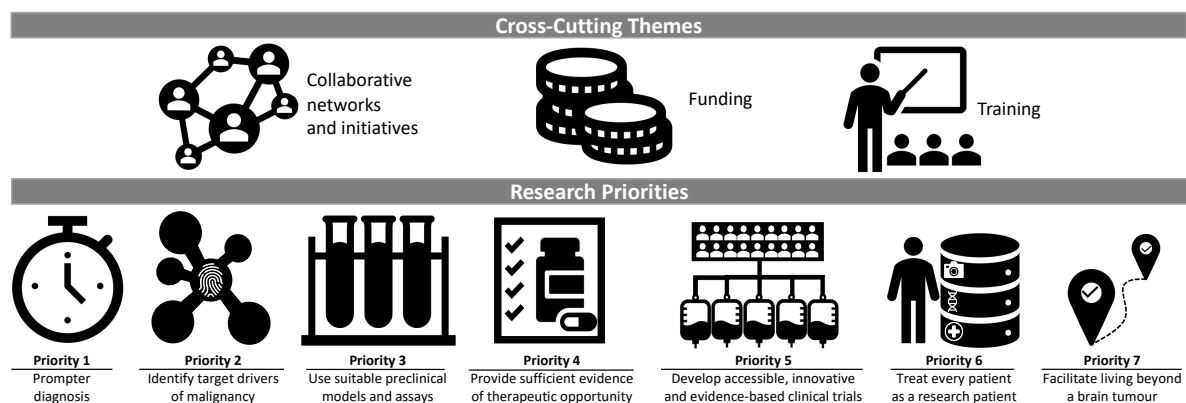


Fig. 1. A schematic outlining the cross-cutting themes and research priorities for brain tumour research in the UK

Cross-cutting themes

Collaborative Networks and Initiatives

The UK is well-placed to lead translational research and innovative trials with global impacts on patient outcomes. The NHS offers a unified healthcare service covering a population of over 60 million, with existing links between cancer centres, neuroscience centres, and academic units. Almost all patients are diagnosed within the NHS allowing for excellent capture and integration of imaging, pathology, and clinical data. Clinical trials are embedded within care pathways and access to trials is increasing via initiatives like NIHR's 'be part of research'¹⁰. UK trials provide true standard of care (SOC) comparator arms in almost all patients owing to the harmonised nature of UK training and clinical practice, including minimal off-label patient-funded drugs, and testing and treatment without requiring health insurance coverage. Primary and post-primary care integration with limited points of entry allows complex queries to be addressed, including patient-oriented research questions and pre-diagnosis journeys.

Since 2018, the UK has developed several clinical/research collaborations. The Tessa Jowell Brain Cancer Mission (TJBCM) is a national initiative supporting clinical studies to provide platforms for facilitating patient enrolment in biomarker-driven trials. Two examples are BRAIN-MATRIX¹¹ and the Minderoo Precision Brain Tumour Programme¹². BRAIN-MATRIX is a 10-centre trial platform (with 4 more centres planned) including advanced molecular profiling, which has recruited 395 patients and provided the basis for several clinical trials (ARISTOCAT, DETERMINE and 5G). The Minderoo Precision Brain Tumour Programme¹² enrolled 230 patients in the first 2 years, exceeding the target of 125 patients, with whole genome and transcriptome sequencing data provided with a 3-week turnaround and a second arm now opening. Other TJBCM programmes include: the Brain Tumour Research Novel

Therapeutics Accelerator (BTR-NTA) which launched in 2023 and aims to de-risk drug or device development by offering up to 240 hours of free (to academics), systematic multidisciplinary evaluation and feedback¹³; NHS clinical neuro-oncology service Centres of Excellence, a designation awarded to 17 UK centres between 2020-2022 (next application round in 2024) to acknowledge standards of excellence in clinical practice, patient care, staff training opportunities, access to clinical trials and research opportunities, which go beyond today's existing guidelines¹⁴; and a dedicated NHS clinical fellowship training programme, which awarded two fellowships in the first round in 2023. Neuro-oncology Research Centres of Excellence have also been funded by CRUK (n=2) and BTR (n=4, with plans for 3 more)¹⁵⁻¹⁷. International networks for pre-clinical and clinical studies include UK members. The global Glioma Longitudinal AnalySiS (GLASS) consortium¹⁸ analyses longitudinal datasets to refine molecular profiling and tumour evolution and includes 3 UK centres, and the Brain Liquid Biopsy Consortium¹⁹ was co-founded in the UK and aims to accelerate research and translation of neuro-oncology biofluid biomarkers. The EORTC Brain Tumour Group is a European-led clinical trial collaborative with UK representation on 6 of its 11 dedicated committees, from which The ROAM/EORTC1308 trial for atypical meningioma was facilitated: a UK-led inter-group trial across 59 sites in the UK, EORTC, and Australia/New Zealand (Trans-Tasman Radiation Oncology Group (TROG))²⁰.

National neuro-oncology conferences are well attended although ideologically segregated – principally oriented toward clinicians (e.g. British Neuro-Oncology Society (BNOS) Annual Conference) or scientists (e.g. CRUK Brain Tumour Conference). Patient and public involvement and engagement (PPIE) in the community is essential. Initiatives such as *braintrust's* Patient Research Involvement Movement (PRIME) bring people closer to research and research closer to funding²¹.

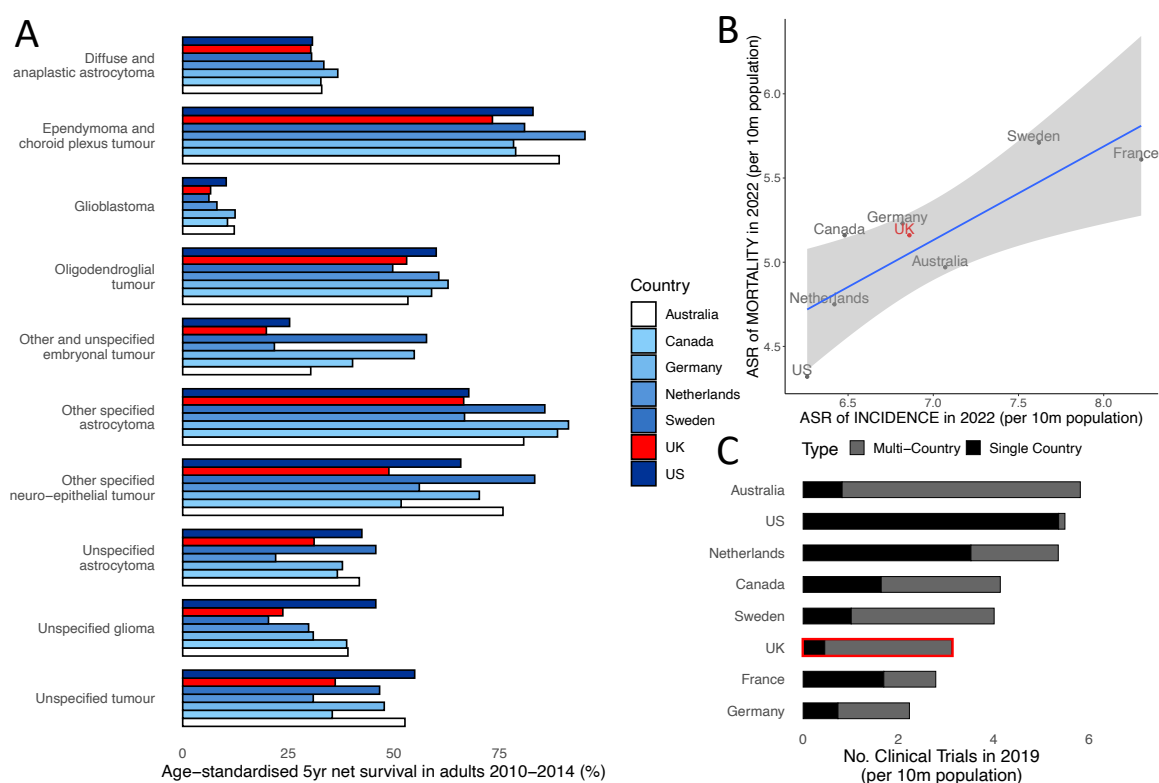


Fig. 2. A) Survival data for brain cancers in different countries⁶ **B)** Age standardised rates (ASR) for brain cancers according to the GLOBOCAN 2022 database version 1.1⁹. The linear regression (blue line) and 95% confidence interval (grey shading) are annotated. **C)** The number of clinical trials that were ongoing in 2019 in different countries⁷.

Recommendations:

- Conferences and events that bring together basic and clinical neuro-oncology, trial methodology expertise, and comprehensive funded PPIE collaboration (SE)
- Clinical trial development in collaboration with international groups (IM)
- Greater collaboration between basic and clinical research, within and between UK centres (IM)
- Integration of accessible and comprehensive biobanking with clinical trial networks (LD)

Brain Tumour Research Funding

Despite recently increasing funding levels for brain cancer research, this disease site remains relatively underfunded. Annual NCRI partner²² funding for brain tumour research increased by £7.4m between 2017 (£10.2m) and 2021 (£17.6m) on par with the increase in funding for breast (£7.0m), bowel (£8.7m) and lung (£6.4m) cancer in the same period (**Fig. 3A**)^{23,24}. However, the funding allocated to brain cancer in 2021 still only constituted 5.5% of the total NCRI partner annual spend on cancer research, having risen from 3.7% in 2017 (**Fig. 3B**)²³. Compare this to breast, bowel and lung cancer for which the allocation has remained consistently high at circa 16%, 12% and 11% of the total budget respectively (**Fig. 3B**)²³. Whilst **Fig. 3A** indicates that funding allocation is proportional to prevalence, this does not take into account the malignancy of each cancer subtype. Indeed, when funding allocation is plotted according to the average years of life lost, brain cancer is a clear outlier^{23,25} (**Fig. 3C**). Inspecting how funding is allocated within cancer subtype, according to the Common Scientific Outline (a 6-tier classification of types of cancer research), we see that a relatively large portion of neuro-oncology research is still focused on understanding the basic biology of the disease, where the more well-funded cancers have more money allocated to earlier detection and prevention research (**Fig. 3D**)²³. This reflects the complexity of tumours of the brain, but also of the organ itself. Numerous factors, including cell type diversity and idiosyncratic aspects of systems biology, has meant that an in-depth knowledge of the human brain still alludes us. Focused, specific research is still very much needed to understand the human brain and its pathologies, including cancer

More, and more targeted, investment is essential with a change in funding mechanisms and opportunities. For example, integrated research funding that spans the pipeline from discovery science, through translation, to clinical research with a focus on improved patient outcomes. The growth of Collaborative Networks and Initiatives highlights a trend towards funding interdisciplinary groups. Encouraging and rewarding interdisciplinary funding, particularly where accessible and inclusive of early career researchers, is vital for truly translational research to be achieved: this means getting treatments to patients, not simply undertaking a series of disconnected preclinical experiments and clinical studies.

Recommendations:

- Brain tumour research should be recognised as a key governmental priority (*cf.* USA Cancer Moonshot) (IM)
- More funders should make brain tumours a strategic focus, prioritising brain tumour-based research that specifically investigates the complexities of this type of cancer in funding calls (IM)
- Ring-fenced funding to support research capacity growth (infrastructure, technology, and people) (IM)
- Increasing the annual investment into brain tumour research to GBP35 million to bring equity with other cancers (LD)
- Facilitate and de-risk collaborative links with private and industry partners to increase funding, drive innovation, and reach the market (LD)

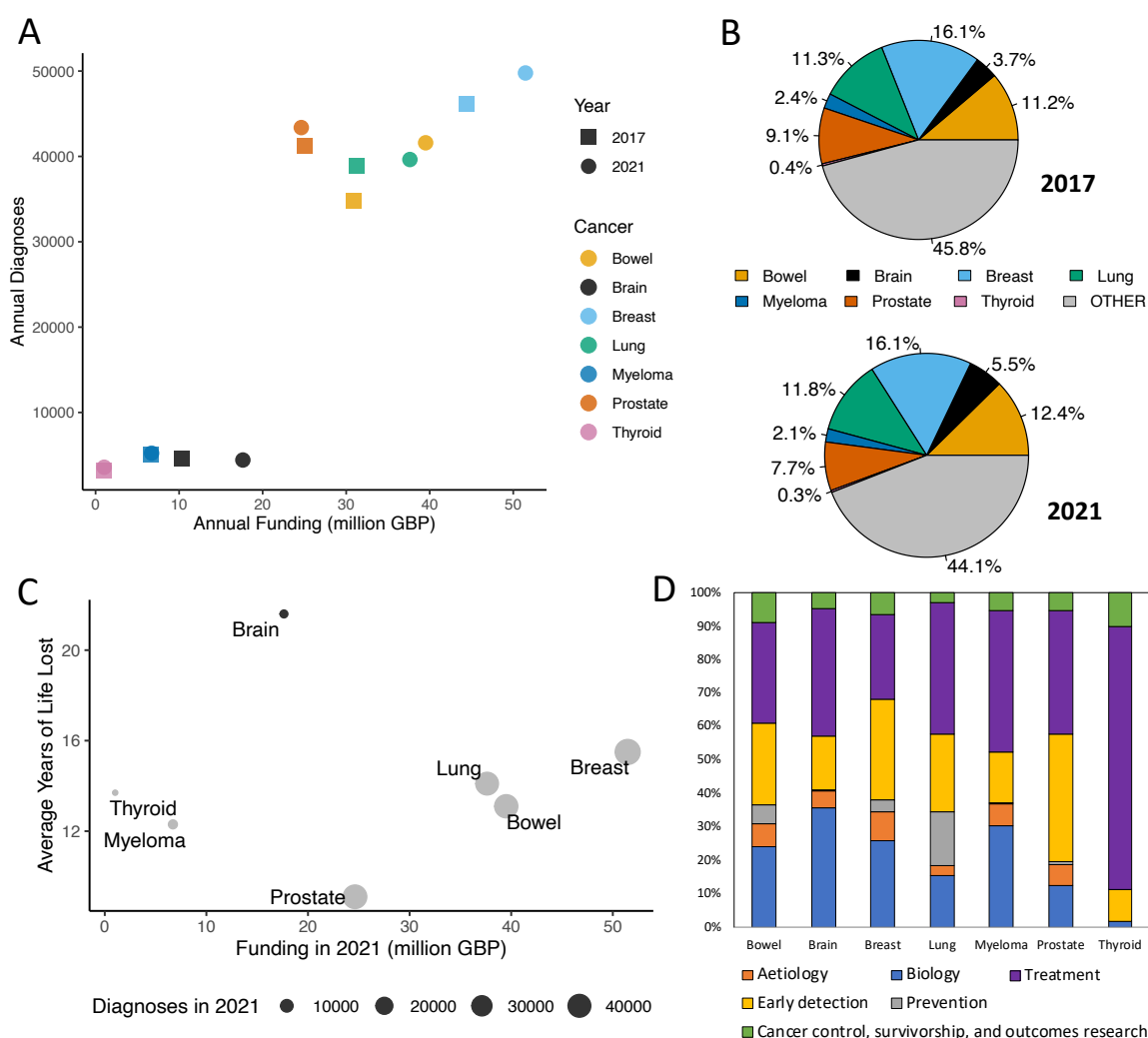


Fig. 3. Data is plotted for some of the most (breast, bowel, lung, prostate) and least (brain, myeloma, thyroid) prevalent cancer subtypes: **A)** The annual research funding allocation by all NCRI partners, plotted according to the number of diagnoses registered, in years ending 2017 and 2021; **B)** The percentage breakdown of the total annual cancer research funding by all NCRI partners for the year ending 2017 (top) or 2021 (bottom); **C)** The annual research funding allocation by all NCRI partners in the year ending 2021 plotted according to the most recently calculated average years of life lost; **D)** The funding allocation by all NCRI partners in the year ending 2021 is broken down according to the percentage spent on each Common Scientific Outline classification of research area.

Neuro-oncology Training (Scientific and Clinical)

Training in scientific neuro-oncology research faces many challenges: brain cancer biology is uniquely complex; the relative disease rarity and accessibility of fresh and fixed tissue limits research samples; and there is no suitable single experimental model nor successful bench-to-bedside trajectory. All 47 UK Masters-level biology programmes with 'cancer' or 'oncology' in the title²⁶ cover generalised elements of pan-cancer research (genomics, immunology, the tumour microenvironment). More specialised cancer-specific research training occurs at the doctoral level, where funding is disproportionately allocated to other cancers. This lack of specific training in, and exposure to, basic neuro-oncology research, combined with lower funding opportunities, produces fewer desirable careers for cancer researchers aiming for independence.

Comparable challenges face clinical training. Increasingly complex management of brain tumours requires surgery, radiotherapy, and chemotherapy. Advances in these fields necessitate

additional ongoing training and development involving multiple specialities. Beyond neurosurgery, where the pathway is well-defined, there is a paucity of training opportunities for neuro-oncology clinicians. UK brain tumour management has, historically, been led by clinical oncologists, with limited time and opportunities to interact with research. Neuro-oncology is not mandatory in the medical oncology curriculum, leading to a scarcity of early-phase trialists and clinical drug developers with the expertise to truly accelerate the development of novel therapeutics for brain tumours.

A joint UK medical/clinical oncology curriculum has been developed to improve interaction and alignment between oncology disciplines, however, neuro-oncology remains optional within this curriculum. Programmes such as the new NIHR/TJBCM Neuro-oncology Fellowship scheme offer intensive interdisciplinary clinical training. Clinical academic programmes in the UK, from the specialised foundation programme to clinical fellowships and lectureships, incorporate higher study. These vary from early, specialty-affiliated (e.g., NIHR Academic Clinical Fellowships) to later, researcher-initiated (e.g., NIHR and other post-doctoral Clinical Lectureships) programmes. However, mid-grade and higher speciality training is already lengthy, and academic programmes and/or higher study extend this. The appropriate balance between clinical and research workloads at the early career consultant level is also unclear. Ringfencing research time is vital for delivering translational research, particularly in key supporting specialities such as pathology, genomic medicine and radiology^{12,27}.

Recommendations:

- High-profile neuro-oncology-focused basic science training initiatives (IM)
- Greater integration between basic and clinical neuro-oncology training programmes (IM)
- Greater research training opportunities for all relevant clinical disciplines with programmes that focus on the skills required to provide high-quality clinical and academic neuro-oncology input (IM)
- New higher speciality fellowships that allow trainees to gain translational experiences in neuro-oncology, combining specialised basic research, clinical trial, and chemo-radiotherapy experience (LD)
- Training plans that facilitate high-level dual training, balancing the demands of a clinical workload and including guidance on securing funding to transition successfully to research independence (LD)
- Support across the intermediate transition to research and clinical independence, with greater flexibility between clinical and research careers and a national commitment to funding early career consultant-level positions to improve recruitment and retention (LD)
- Safeguarding research time for senior clinical researchers, with greater stakeholder interactions between the NHS, Royal Colleges, and academic institutions (LD)

Research Priorities

Priority 1: Prompter diagnosis

In many cancers, the notion of an ‘early diagnosis’ pertains to identifying the disease in a less mature state (at a lower ‘stage’ or ‘grade’), which can lead to less intrusive/toxic and/or more effective treatment. In brain cancer, it is debatable whether diagnosing at *earlier* disease stages impacts treatment decisions and prognosis. However, it is widely accepted that a *prompter* diagnosis i.e. shorter time between the development of symptoms of a tumour, irrespective of its stage or grade, and clinical confirmation of the presence and type of tumour, is beneficial for many reasons²⁸⁻³⁰. Brain tumours are challenging to diagnose, with idiosyncrasies and barriers at each level from initially detecting a brain tumour through to the diagnosis of subtype³¹. Presenting symptoms are driven both by tumour anatomical location and more global effects of tumour growth. The former may produce stereotypical motor, visual, or speech deficits but the latter are non-specific and secondary to raised intracranial pressure or regional changes caused by the tumour e.g. headaches, nausea/vomiting,

lethargy, behavioural changes, or seizures. The commonality of some non-specific symptoms often delays patients visiting a doctor until symptoms escalate. Once consulted, medical practitioners often pursue other more common diagnoses, delaying definitive investigations. Rationing of investigations such as brain imaging also delays diagnosis. Approximately 2/3 of brain tumours are diagnosed after an emergency admission to hospital often preceded by several primary care consultations.³² Only 1% of patients are diagnosed through the designated NHS England two-week wait suspected cancer pathway³³. Campaigns such as 'HeadSmart' (The Brain Tumour Charity), 'Brain Tumour Awareness Month', and 'Wear a Hat Day' (Brain Tumour Research) are increasing awareness of brain tumour symptoms with the aspiration of leading to prompter diagnosis.

Once the presence of a brain tumour is established, there are subsequent challenges to timely categorisation. Complementing histopathological assessment, molecular characterisation is central to brain tumour diagnostic classification³⁴. Genomics England and NHS England are working to address issues with the speed of, and access to, genomic testing. Despite establishing Genomic Laboratory Hubs in England, there is social and regional inequality in access to molecular profiling across the UK with inconsistencies in infrastructure, resourcing, funding, and training. More research is needed to enable prompter diagnosis, such as liquid biopsy, which could be used as part of a primary care work-up³⁵, perhaps even at the point of care.

Recommendations:

- Work with the Tessa Jowell Equity in Genomics Working group to improve UK-wide access to genomic testing (SE)
- Training in the requirements and provision of sufficient biological material for diagnosis including molecular profiling with standardisation of sample submission processes (SE)
- Increase public and healthcare provider awareness of brain tumour symptoms (IM)
- Coordinate with genomic hubs to ensure timely, standardised, easily clinically interpretable reports (IM)
- Improve direct access to brain imaging from primary care (IM)
- Develop novel, non-invasive tools for prompter diagnosis (LD)

Priority 2: Identify actionable target drivers of malignancy

Whilst molecular testing is being adopted for the diagnostic classification of brain tumours (Priority 1), the results do not routinely inform treatment decisions because of limited therapeutically actionable molecular biomarkers. This results from a limited understanding of genomics of brain tumours, and the (historical) exclusion of patients with brain tumours from precision medicine targeted trials.

Access to high-quality, well-annotated patient biosamples is essential for identifying target drivers of malignancy, particularly when co-occurring driver genes typically activate different collaborating oncogenic pathways. Integrating genomic, epigenomic, transcriptomic, proteomic and neuroimaging data will be critical to reveal vulnerabilities most amenable to therapeutic targeting. Disease rarity makes neuro-oncology biobanking relatively costly because the infrastructure needed is disproportionate to the sample volumes. The resulting sample scarcity for research causes issues of ownership and access to existing collections. Furthermore, brain bio-banking is often under-resourced, leading to deficits in: processing to maximise sample usage; collection beyond the tumour (host, blood, CSF); associated clinical metadata with follow-up; and generation of associated patient-derived models (see Priority 3). This promotes a negative perception of myriad biobanked samples sitting unavailable for research, when samples are either not known about, are inaccessible, or lack sufficient clinical annotation for utility. Even where additional research-allocated samples cannot be collected, making the genetic data resulting from clinical practice accessible to basic science researchers, alongside linked clinical metadata and imaging data, would be hugely valuable.

In the UK, several initiatives aim to tackle this. BRAIN UK (BRain Archive Information Network UK)^{36,37} is a virtual biobank across a network of NHS Neuropathology Centres, exemplifying the unique

UK ability to leverage NHS connectivity. BRAIN UK has generic ethics needed to approve projects and coordinate and grant access to archival surplus brain material. However, this is mostly limited to fixed tissue and retrospectively collated, centre-specific clinical data owing to a dearth of local infrastructure for greater provision. BRAIN MATRIX³⁸ includes resources to perform a more limited collection of frozen adult glioma samples, specifically, and molecularly profile them via NHS England Genomic Hubs with linked imaging and clinical data. While centralised tissue cannot be repurposed, there is no barrier to using fresh tissue at the site for complementary research techniques such as single-cell analyses. Again, this is dependent on local infrastructure. Alongside these national efforts, multiple autonomous UK research tissue banks include neuro-oncology collections. These independent efforts vary with regard to consenting procedures, types of samples and data collected, access, processing, governance, and application requirements. Their coordination would better facilitate higher-impact, larger-scale research.

Identification of target drivers relies on access to raw data linked to the clinically annotated samples and their originating experiments. Dataset generation is often research group-specific, requiring significant effort and funding. Academic dissemination and recognition routes discourage rapid sharing of core datasets or timely raw data release. Dataset release should itself be a suitably credited research output, with appropriate embargoed data usage to protect the originating study. International efforts such as The Cancer Genome Atlas³⁹ and GLASS¹⁸ have championed timely data sharing.

Recommendations:

- Develop infrastructure where every patient with brain cancer can contribute to a biobank, with clinically available molecular testing, and integrate this with clinical trials (LD)
- Harmonise and consolidate brain tumour tissue banking (**Table 1**) via infrastructure funding to improve accessibility and availability of linked samples, imaging, and clinical data (LD)
- Where appropriate, support the transfer of routinely collected samples and data to safe havens and trusted research environments with suitable governance (LD)
- Expect and encourage return and linkage of suitable datasets produced from downstream sample and data processing, partly by making the release of such datasets an appropriately recognised academic output (LD)

Table 1 Specific recommendations for UK biobanking

Biobanking Aspect	Recommendations
Ethical approval	Harmonised across multiple sites
	Self-governing with generic ethical approval (i.e. applicant does not require project-specific ethical approval)
	Include all forms of analysis (genetic, <i>in vivo</i> , model generation)
	Include industry access with associated cost recovery
	Include fair usage clauses
Informing and consenting patients	Informing and consenting patients should be embedded within the clinical pathways following engagement with neurosurgeons, neuropathologists and neuroradiologists
	Standardised, inclusive information giving (videos) and forms in multiple languages
	Centralised, accessible recording of consent across multiple sites
Resourcing	Multidisciplinary RTBs can link with other disease sites, with potential convergence in pathology departments
	Tiered collection sites would enable biobanking with fewer resources where necessary
Sample Processing	Collection of blood, CSF, saliva, FFPE, fresh tissue

	Harmonised processing SOPs
	Enable future proofing (e.g. single-cell storage)
	Centralised recording of samples across multiple sites
Data Collection	Standardised prospective data collection to include imaging data
	Post-surgery data acquisition at regular intervals to capture short-term (e.g. diagnostic test results) and long-term (e.g. survival) follow-up data
	Adherence to FAIR principles - https://www.go-fair.org/fair-principles/
Access	Live, open-access database of samples available with forthcoming release schedules
	Unrestricted yet audited access to researchers following suitably reviewed, user-friendly application process
	Access to industry via suitable contractual agreement and cost-recovery

Priority 3: Use suitable preclinical models and assays

Experimental models are needed to: 1) validate the direct involvement of aberrant molecules and/or mechanisms in pathogenesis as causative rather than consequent for rational prioritisation of drug development; 2) screen novel therapeutic interventions. Both require the experimental system to mirror patient biology, or the specific aspect being tested, and this poses a major challenge for brain tumours⁴⁰. The continued failure of neuro-oncology clinical trials is partly attributable to difficulties in experimentally modelling brain tumour biology i.e. tumour heterogeneity; tumour microenvironment (TME); the blood-brain barrier (BBB); and response to standard of care (SOC)^{3,41}. Advances in brain cancer cell culture techniques have led to cell lines that more closely mirror the originating tumour⁴². These can be used in 2D and 3D systems, with scaffolds and co-cultures to incorporate the TME, and *in vivo*, but each system models different aspects of tumour biology, and increasing complexity increases time and cost, forcing trade-offs⁴³⁻⁴⁶. Organoids and microfluidic *ex vivo* and BBB models offer great promise for modelling complexity at scale⁴⁷⁻⁴⁹. Patient-derived xenotransplants (PDX) models usually do not fully recapitulate the TME.

Most UK institutes cannot derive their own brain cancer models, and there are significant overheads associated with subsequent genomic and phenotypic characterisation. The CRUK-funded Glioma Cellular Genetics Resource (GCGR)⁵⁰ was established to provide state-of-the-art well-characterised cell lines to researchers and industry, but such resources are hard to sustain. Developing and optimising new models is difficult and laborious, precluding any one group from incorporating a full range into their repertoire. In 2021, the British Neuro-Oncology Society completed a UK survey of preclinical neuro-oncology models to identify commonly adopted approaches and highlight groups that are willing to collaborate with and train other researchers⁵¹. However, barriers to cross-institutional working, difficulty in retaining ownership (intellectual property), and a lack of infrastructure and resource funding vastly reduces the impetus to share models across research groups⁵². GlioModel⁵³ is a UK-based initiative to develop a preclinical modelling resource, specifically for target validation in glioblastoma and make it accessible through fee-for-service, although self-sustainability remains uncertain.

Recommendations:

- Underpin initiatives like the GCGR and GlioModel with infrastructure funding that widens accessibly and ensures longevity⁵² (SE)
- Standardise model characterisation with regards to molecular profiles, phenotypes, and response to current SOC (IM)
- Tiered approaches to target validation and drug screening are needed, with cascades of models and assays on a range of scales and complexities, based on the strength of evidence for, or biology underlying, the specific target or drug (IM)

- Evolve academic recognition. Researchers focused on model development should be credited on outputs where their models are used while retaining the primacy of the molecule, mechanism, or hypothesis being tested (LD)

Priority 4: Provide sufficient evidence of therapeutic opportunity

The adoption of temozolomide as the standard of care for glioblastoma occurred almost 20 years ago², demonstrating the translational failure which casts neuro-oncology as a ‘graveyard’ for novel therapeutics. Among legion contributors, inter- and intra-patient heterogeneity of brain cancer and the blood-brain barrier, which modulates drug delivery, represent major obstacles⁵⁴. Academic research is key to identifying new drug targets (Priority 2), including understanding target biology and links between targets and disease states (Priority 3). However, academic credit and pharmaceutical company value structures do not align. Academic progression prioritises publication and grant funding, often predicated on novelty, while industry prioritises understanding the “right target” which requires thorough, standardised validation (or de-validation) of a scientific hypothesis throughout the lifetime of a project. Furthermore, the ability to de-risk a promising drug target is dependent on the clinical annotation, quantity/quality of patient tissue, and accuracy of the model(s) used in its validation/de-validation. There are problems in both aspects of neuro-oncology research.

Several biopharma companies have adopted the 5R framework (“the right target, right tissue, right safety, right patient, and right commercial potential”) to tackle R&D productivity issues^{55,56}. To deliver impactful data packages that can serve as a platform of evidence for the next stages of drug development, research must progress from purely academic exploration to the initiation of efforts to interrogate the drug candidate in the context of pharmacokinetic/pharmacodynamic properties, establishing proof of concept as well as safety/tolerability,^{55,57,58}.

The BTR-NTA aims to review and guide the translation and development of novel treatments by an international multidisciplinary group of experts. Independent, transparent advice will help researchers translate a candidate compound that can be rapidly taken forward into clinical trials for patients, optimising trial design, and maximising the likelihood of success¹³.

Recommendations:

- Synergise academic research and pharmaceutical company requirements via the integration of industry experts into research planning, funding applications, and dissemination events (SE)
- Integration of industry expertise and experiences into neuro-oncology training programmes (perhaps industry experience for research fellows) and consortia (IM)
- Communicate with industry experts on how to overcome intellectual property barriers to facilitate closer working relationships between academic and big biopharma (LD)

Priority 5: Develop accessible, innovative, and evidence-based clinical trials

Clinical trials realise translation of novel interventions arising from Priorities 2-4. First-in-man phase 1 trials evaluate safety and test pharmacokinetics with escalated dosing to ascertain the appropriate prescription. Phase 2 trials apply this to a larger cohort to assess safety and indicate activity. Large, randomised phase 3 trials test promising interventions, usually against SOC. This pipeline has limitations for rarer cancers, as reflected in the poor conversion of promising early brain cancer trial results to phase 3 outcomes, and the lack of improvement in overall survival since 2005 (**Table 2**). Some contributing factors are relevant to all clinical trials with others brain cancer specific.

Firstly, patients with brain tumours are excluded from the majority of early phase trials, and tumour agnostic basket trials with <1% of UK recruiting trials listed on the EC trial finder website⁵⁹ permitting enrolment of patients with brain tumours. This has historically been attributed to a poor understanding of the blood-brain barrier (and its leakiness) and uncertainty about whether novel agents can achieve meaningful concentrations in the brain. Phase 0 window of opportunity trials which can quantify brain exposure to novel agents, as well as provide pharmacodynamic evidence of

pathway modulation will help to identify active drugs more efficiently, but they are challenging to deliver.

Early phase trials, particularly single-arm trials, typically have small sample sizes which risk selection and sampling bias and increased risk of false positives. If surrogate endpoints do not correlate with clinical outcomes, they can mislead causing premature and inappropriate inclusion/exclusion of candidate interventions. Surrogate biomarkers are lacking and there is variability of surgery and radiotherapy, varying by tumour location and proximity to eloquent brain and organs at risk, which limits comparator arm comparability. Given the heterogeneity of brain cancers, even where targeted agents have been trialled in brain cancer patients, and progressed to later-stage registration trials, these have been in an *unselected* patient population and failed to meet their endpoints (Table 2). Even with an adaptive clinical trial strategy such as those used in the international Phase 2/3 platform GBM AGILE trial (NCT03970447), evaluating multiple regimes in *unselected* patients has been disappointing thus far with the initial regimes tested not meeting interim efficacy for transition to Phase 3⁶⁰. This suggests an urgent and ambitious need for bespoke novel clinical trial designs to specifically overcome the challenges specific to brain tumour trials incorporating a seamless transition from Phase 0 surgical trials to biomarker-defined early-phase hypotheses testing to later-stage efficacy testing. The MHRA-approved 5G (An AGile Next Generation Genomically Guided Glioblastoma Trial) adaptive platform trial (conceived following the NCRI Brain Strategic Workshops in 2021) will utilise genomic and transcriptomic data to stratify patients into molecular hypotheses testing subprotocols, allowing for agile and rapid *in-flight course correction* and refinement of molecular hypotheses as investigators learning as much as they can directly from patients enrolled on this platform.

Clinical trial patients commonly do not reflect the wider patient population, with older or comorbid patients underrepresented⁶¹. Trial design will need to be pragmatic eschewing small-scale, single-centre and/or single-arm interventions in favour of cross-centre collaboration and/or multi-arm settings, to ensure the widening of patient access to biologically appropriate clinical trials and the swifter generation of real-world meaningful data impacting patient outcomes. Patient-centred outcomes will need to be at the core of all trials.

Table 2: Clinical outcomes of the major phase 3 randomised controlled trials (RCTs) from 2002-2022 for newly diagnosed glioblastoma.

Authors	Year	Intervention	PFS (months)	OS (months)	Change in clinical practice?
<i>Unselected</i>					
Stupp et al. ²	2005	Radiotherapy + Temozolomide (n=287) Radiotherapy (n=286)	6.9 5.0	14.6 12.1	Yes
Gilbert et al. ⁶²	2014	Bevacizumab + STUPP (n=312) STUPP (n=309)	10.7 7.3	15.7 16.1	No
Chinot et al. ⁶³	2014	Bevacizumab + STUPP (n=458) STUPP (n=463)	10.6 6.2	16.8 16.7	No
Stupp et al. ⁶⁴	2014	Cilengitide + STUPP (n=272) STUPP (n=273)	10.6 7.9	26.3 26.3	No
Westphal et al. ⁶⁵	2015	Nimotuzumab + STUPP (n=71) STUPP (n=71)	7.7 5.8	22.3 19.6	No
Weller et al. ⁶⁶	2017	Rindopepimut + STUPP (n=371) STUPP (n=374)	8.0 7.4	20.1 20.0	No
Stupp et al. ⁶⁷	2017	TTF + STUPP (n=466)	6.7	20.9	Yes*

		STUPP (n=229)	4.0	16.0	
<i>Biomarker selected</i>					
Herrlinger et al. ⁶⁸	2019	<i>Methylated MGMT</i> Lomustine + STUPP (n=66) STUPP (n=63)	16.7 16.7	48.1 31.4	No
Lim et al	2022	<i>Methylated MGMT</i> Nivolumab + STUPP STUPP	10.6 10.3	28.9 32.1	No
Lassmann et al	2023	<i>EGFR amplified (FISH)[#]</i> STUPP + Depatux-M (323) STUPP (n=316)	8.0 6.3	18.9 18.7	No

PFS = progression-free survival; OS = overall survival; STUPP = Fractionated radiotherapy with concomitant and adjuvant Temozolomide; TTF = Tumour Treating Fields; *in some healthcare settings (not approved by NICE in UK based on failure to meet QALY threshold); [#]EGFR FISH assay selected for both EGFR WT and EGFRvIII amplified tumours which were included in the study despite the binding domain for Depatux-M being lost in EGFRvIII.

Recommendations:

- Prioritise research and validation of reliable intermediate or surrogate markers, including biomarkers, that can be used to guide early interim stop/go decision-making for novel interventions, and which may translate as companion diagnostics for rational clinical delivery (IM)
- Adopt innovative early-phase clinical trial designs (e.g., window, basket, umbrella, platform) that have been successful in other tumours (IM)
- Prioritise precision medicine approaches with brain penetrant agents to develop a stratified personalised approach for brain tumours (LD)
- Champion the inclusion of patients with brain tumours in early-phase clinical trials/basket trials of novel agents with biological rationale (LD)
- Ambitious scaling up of clinical trial availability aiming for every patient with brain cancer to have access to clinical trials (LD)

Priority 6: Treat every patient as a research patient

Only 5% of brain tumour patients are entering the limited number of trials available, partly from a lack of up-to-date clinical trial databases but also the variability in access. The latter results from cross-centre variation in infrastructure, resources, and capacity, including time allocation for the trial leads and research nurse support. Improving outcomes needs the right people to drive change, requiring sufficient time allocation and remuneration. This is unsustainable: recruitment and retention of (clinical) academics requires suitable rewards. In addition, whilst some may not be eligible for trials, every patient should be offered to opportunity to donate samples, imaging and clinical metadata to research.

The analysis and interpretation of outcome measures, low adherence, and missing data are methodological challenges. The current focus on system-wide delivery and outcome measurement loses sight of the person living with the brain tumour and devalues what matters to them. Patients are more than their clinical data: e.g. their perception of their health, what motivates or negates behaviour changes, or how other life events and stressors confound the maintenance of health and well-being. Yet patient involvement in research remains fragmented and lacks strategic overview. The multiplication of therapies means more trials, necessitating a paradigm shift in the measurement of health-related quality of life (HRQoL). The disproportionate focus on outcomes limits understanding of what individual patients want to achieve. COBRA and COSMIC are patient-centred clinical trials co-developed with patient and carer stakeholders that are starting to move these goalposts, ensuring

that outcome sets are truly meaningful to patients in the real world^{69,70}. With personalised medicine, patients experience different clinical journeys: one size no longer fits all.

High rates of physical and cognitive morbidity require alternative supportive interventions to address the impact of the tumour and its treatment^{71,72}. Challenges with discerning tumour-driven and treatment-driven symptoms are compounded by uncertain disease trajectories. Symptoms cover a broad spectrum: people can exhibit apathy and indifference through to egocentrism, disinhibition, and aggression. Decline can be insidious or take only weeks, and tools to measure it, while validated, are not universal necessitating multiple assessments in a variety of forms.

Recommendations:

- To ensure meaningful involvement, it is important to consider “how much” patient involvement is included but also “how, why, and when” (IM)
- Encourage availability and comparability of routine healthcare data to facilitate “care-based evidence” to complement evidence-based care (IM)
- Increase trial delivery capacity across the UK by improving infrastructure (LD)
- Every patient is a research patient, for their whole trajectory, for all brain tumours (LD)

Priority 7: Facilitate living beyond a brain tumour

The UK is strategically well-placed to contribute to and lead research into survivorship, quality of life, and patient-reported outcomes⁷³. Several centres have produced world-leading outputs in the last decade with international collaborators. The James Lind Alliance produced a consensus priority list highlighting ‘quality of life’ questions about lifestyle factors, interval scanning, early referral to palliative care, the study of late effects, interventions for carers, and strategies for managing fatigue⁴. Numerous routes for grant funding exist: The Brain Tumour Charity’s dedicated Quality of Life research grant call funded BT-LIFE, an innovative UK pilot trial of lifestyle interventions for fatigue that recently published positive results⁷⁴, and the NIHR funded SPRING, a phase 3 trial of levetiracetam prophylaxis of epilepsy in seizure-naïve patients with newly-diagnosed glioma⁷⁵.

Notwithstanding these UK initiatives, survivorship and outcomes research received just 5% of total NCRI partner spend on brain tumour research in 2021 (**Fig. 3D**), potentially limiting improvements. Increasing proportional spending requires a shift away from low-impact observational studies. Although single-centre observational studies are more accessible to trainees or non-career academics, their analysis is typically confounded by the high number of variables and small sample sizes. The clinical impact of observational studies is limited and these proposals struggle to attract funding. Large-scale, collaborative epidemiology or data-linkage studies and RCTs are robust to these limitations and should be prioritised. Glioma patients also have cognitive impairment, fatigue, and complex often toxic treatments that can directly and indirectly affect quality of life. Challenges to clinical trials in these areas require strong mentorship and guidance to support and improve the methodological quality of proposals.

Horizon scanning predicts an increase in early-phase intervention trials (especially non-pharmacological) to improve survivorship quality of life. In anticipation, we must investigate how to encourage behavioural change in brain tumour patients, so that effective interventions can be implemented.

Recommendations:

- Remunerate clinicians to lead research by increasing the number of UK grant schemes that cover a proportion of PI salary (SE)
- Shift metrics from preserving life to enhancing life (SE)
- Engage with funders to encourage and develop calls prioritising large-scale epidemiology and RCTs (IM)
- Leverage existing infrastructure and networks to increase multicentre collaborations (IM)
- Quality of life research is key, compelling a shift from decision-sharing to option-sharing (IM)

Conclusion

Brain cancer is arguably the worst form of cancer, owing to dismal prognosis and often severe impacts on quality of life. There are inherent challenges to brain tumour research, owing to the complex nature of the disease, that are shared worldwide. The UK is densely populated and has a unique healthcare system, potentially providing the opportunity to address, and even overcome, some of these challenges. Whilst there will be key similarities and shared challenges for paediatric brain tumour research in the UK, it is noted that there will also be significant differences and unique bottlenecks that have not been covered herein. We hope that the recommendations made in this position paper can inspire UK reform, and provide focal points for future UK funding calls and partnerships, to accelerate progress towards better and longer life for adult brain cancer patients across the whole world.

References

1. Cancer Research UK. Brain, other CNS and intracranial tumours statistics. Accessed 22nd March, 2023. <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/brain-other-cns-and-intracranial-tumours>
2. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. Mar 10 2005;352(10):987-96. doi:10.1056/NEJMoa043330
3. Aldape K, Brindle KM, Chesler L, et al. Challenges to curing primary brain tumours. *Nat Rev Clin Oncol*. Aug 2019;16(8):509-520. doi:10.1038/s41571-019-0177-5
4. National Institute of Health Research: James Lind Alliance. Neuro-oncology. Accessed 22.12.2022, <https://www.jla.nihr.ac.uk/priority-setting-partnerships/neuro-oncology/>
5. Brain Tumour Research. All-Party Parliamentary Group on Brain Tumours. Accessed 26th March 2023, 2023. <https://www.braintumourresearch.org/campaigning/appg-on-brain-tumours>
6. Girardi F, Matz M, Stiller C, et al. Global survival trends for brain tumors, by histology: analysis of individual records for 556,237 adults diagnosed in 59 countries during 2000-2014 (CONCORD-3). *Neuro Oncol*. Mar 14 2023;25(3):580-592. doi:10.1093/neuonc/noac217
7. Kong BY, Carter C, Nowak AK, et al. Barriers and potential solutions to international collaboration in neuro-oncology clinical trials: Challenges from the Australian perspective. *Asia Pac J Clin Oncol*. Jun 2022;18(3):259-266. doi:10.1111/ajco.13606
8. Brain GBD, Other CNSCC. Global, regional, and national burden of brain and other CNS cancer, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. Apr 2019;18(4):376-393. doi:10.1016/S1474-4422(18)30468-X
9. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. May 2021;71(3):209-249. doi:10.3322/caac.21660
10. National Health Service. Be Part of Research. Accessed 22nd March, 2023. <https://bepartofresearch.nihr.ac.uk/results/search-results>
11. Watts C, Savage J, Patel A, et al. Protocol for the Tessa Jowell BRAIN MATRIX Platform Study. *BMJ Open*. Sep 8 2022;12(9):e067123. doi:10.1136/bmjopen-2022-067123

- 617 12. Cancer Research UK. *Creating Time for Research*. 2021.
618 [https://www.cancerresearchuk.org/sites/default/files/creating_time_for_research_februar](https://www.cancerresearchuk.org/sites/default/files/creating_time_for_research_februar_y_2021_-_full_report-v2.pdf)
619 [y 2021 - full report-v2.pdf](https://www.cancerresearchuk.org/sites/default/files/creating_time_for_research_februar_y_2021_-_full_report-v2.pdf)
- 620 13. Tessa Jowell Brain Cancer Mission. Brain Tumour Research Novel Therapeutics
621 Accelerator (BTR-NTA). Accessed 24th March, 2023.
622 <https://www.tessajowellbraincancermission.org/strategic-programmes/btr-nta/>
- 623 14. Tessa Jowell Brain Cancer Mission. Tessa Jowell Centre of Excellence for Adults.
624 [www.tessajowellbraincancermission.org/strategic-programmes/tessa-jowell-centres-of-](http://www.tessajowellbraincancermission.org/strategic-programmes/tessa-jowell-centres-of-excellence)
625 [excellence](http://www.tessajowellbraincancermission.org/strategic-programmes/tessa-jowell-centres-of-excellence)
- 626 15. University of Edinburgh. CRUK Brain Tumour Centre of Excellence. Accessed 22nd
627 March, 2023. <https://www.ed.ac.uk/cancer-centre/cruk-brain-tumour-centre-of-excellence>
- 628 16. University College London. CRUK Brain Tumour Centre of Excellence.
629 [https://www.ucl.ac.uk/cancer/research/centres-and-networks/cruk-brain-tumour-centre-](https://www.ucl.ac.uk/cancer/research/centres-and-networks/cruk-brain-tumour-centre-excellence/cruk-brain-tumour-centre)
630 [excellence/cruk-brain-tumour-centre](https://www.ucl.ac.uk/cancer/research/centres-and-networks/cruk-brain-tumour-centre-excellence/cruk-brain-tumour-centre)
- 631 17. Brain Tumour Research. Brain Tumour Research Centres of Excellence.
632 <https://www.braintumourresearch.org/research/centres-of-excellence>
- 633 18. The GLASS Consortium. Glioma through the looking GLASS: molecular evolution of
634 diffuse gliomas and the Glioma Longitudinal Analysis Consortium. *Neuro-Oncology*.
635 2018;20(7):873-884. doi:10.1093/neuonc/noy020
- 636 19. Brain Liquid Biopsy Consortium. Brain Liquid Biopsy Consortium. Accessed 23rd Aug,
637 2023. <https://brainlbc.org>
- 638 20. Jenkinson MD, Javadpour M, Haylock BJ, et al. The ROAM/EORTC-1308 trial: Radiation
639 versus Observation following surgical resection of Atypical Meningioma: study protocol for a
640 randomised controlled trial. *Trials*. Nov 14 2015;16:519. doi:10.1186/s13063-015-1040-3
- 641 21. brainstrust. Patient Research Involvement Movement (PRIME). Accessed 22nd March,
642 2023. <https://brainstrust.org.uk/about-brainstrust/brain-tumour-research/prime/>
- 643 22. National Cancer Research Institute. Our Partners. Accessed 25th March, 2023.
644 <https://www.ncri.org.uk/about-us/our-partners/>
- 645 23. NCRI. Cancer Research Database. 4th March 2024, [https://www.ncri.org.uk/how-we-](https://www.ncri.org.uk/how-we-work/cancer-research-database/)
646 [work/cancer-research-database/](https://www.ncri.org.uk/how-we-work/cancer-research-database/)
- 647 24. Statistics OfN. Cancer registration statistics, England.
648 [https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsa](https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland)
649 [nddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland](https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland)
- 650 25. Ahmad AS, Offman J, Delon C, North BV, Shelton J, Sasieni PD. Years of life lost due to
651 cancer in the United Kingdom from 1988 to 2017. *Br J Cancer*. Nov 2023;129(10):1558-1568.
652 doi:10.1038/s41416-023-02422-8
- 653 26. FindAUniversity Ltd. FindAMasters. Accessed 22.12.2022.
654 <https://www.findamasters.com>
- 655 27. Corrected oral evidence: Clinical academics in the NHS (2022).

- 656 28. brainstrust. *Earlier, prompt or faster diagnosis of a brain tumour?* 2023.
657 [https://c6q4s2z2.rocketcdn.me/wp-content/uploads/2023/03/brainstrust-faster-diagnosis-](https://c6q4s2z2.rocketcdn.me/wp-content/uploads/2023/03/brainstrust-faster-diagnosis-27.03.23-1.pdf)
658 [27.03.23-1.pdf](https://c6q4s2z2.rocketcdn.me/wp-content/uploads/2023/03/brainstrust-faster-diagnosis-27.03.23-1.pdf)
- 659 29. The Brain Tumour Charity. *Brain Tumours: Fighting for Faster Diagnosis.* 2023.
660 [https://assets.thebraintumourcharity.org/live/uploads/2023/03/Brain-Tumours-Fighting-](https://assets.thebraintumourcharity.org/live/uploads/2023/03/Brain-Tumours-Fighting-for-Faster-Diagnosis.pdf)
661 [for-Faster-Diagnosis.pdf](https://assets.thebraintumourcharity.org/live/uploads/2023/03/Brain-Tumours-Fighting-for-Faster-Diagnosis.pdf)
- 662 30. National Cancer Research Institute. *Position Statement on Early Diagnosis of Brain*
663 *Tumours.* 2023. [https://www.ncri.org.uk/wp-content/uploads/NCRI-Brain-Group-Position-](https://www.ncri.org.uk/wp-content/uploads/NCRI-Brain-Group-Position-Paper-2023.pdf)
664 [Paper-2023.pdf](https://www.ncri.org.uk/wp-content/uploads/NCRI-Brain-Group-Position-Paper-2023.pdf)
- 665 31. Walker D, Hamilton W, Walter FM, Watts C. Strategies to accelerate diagnosis of
666 primary brain tumors at the primary-secondary care interface in children and adults. *CNS*
667 *Oncol.* Sep 2013;2(5):447-62. doi:10.2217/cns.13.36
- 668 32. Penfold C, Joannides AJ, Bell J, Walter FM. Diagnosing adult primary brain tumours:
669 can we do better? *Br J Gen Pract.* Jun 2017;67(659):278-279. doi:10.3399/bjgp17X691277
- 670 33. Elliss-Brookes L, McPhail S, Ives A, et al. Routes to diagnosis for cancer - determining
671 the patient journey using multiple routine data sets. *Br J Cancer.* Oct 9 2012;107(8):1220-6.
672 doi:10.1038/bjc.2012.408
- 673 34. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the
674 Central Nervous System: a summary. *Neuro-Oncology.* 2021;23(8):1231-1251.
675 doi:10.1093/neuonc/noab106
- 676 35. Brennan PM, Butler HJ, Christie L, et al. Early diagnosis of brain tumours using a novel
677 spectroscopic liquid biopsy. *Brain Commun.* 2021;3(2):fcab056.
678 doi:10.1093/braincomms/fcab056
- 679 36. Nicoll JAR, Bloom T, Clarke A, Boche D, Hilton D. BRAIN UK: Accessing NHS tissue
680 archives for neuroscience research. *Neuropathol Appl Neurobiol.* Feb 2022;48(2):e12766.
681 doi:10.1111/nan.12766
- 682 37. University of Southampton. BRAIN UK. Accessed 30.01.2023,
683 <https://www.southampton.ac.uk/brainuk/about/index.page>
- 684 38. University of Birmingham. Tessa Jowell BRAIN MATRIX. Accessed 30.01.2023,
685 <https://www.birmingham.ac.uk/research/crcu/trials/brain-matrix/index.aspx>
- 686 39. Cancer Genome Atlas Research N. Comprehensive genomic characterization defines
687 human glioblastoma genes and core pathways. *Nature.* Oct 23 2008;455(7216):1061-8.
688 doi:10.1038/nature07385
- 689 40. Rominiyi O, Al-Tamimi Y, Collis SJ. The 'Ins and Outs' of Early Preclinical Models for
690 Brain Tumor Research: Are They Valuable and Have We Been Doing It Wrong? *Cancers (Basel).*
691 Mar 25 2019;11(3)doi:10.3390/cancers11030426
- 692 41. Akter F, Simon B, de Boer NL, Redjal N, Wakimoto H, Shah K. Pre-clinical tumor models
693 of primary brain tumors: Challenges and opportunities. *Biochim Biophys Acta Rev Cancer.* Jan
694 2021;1875(1):188458. doi:10.1016/j.bbcan.2020.188458
- 695 42. Lee J, Kotliarova S, Kotliarov Y, et al. Tumor stem cells derived from glioblastomas
696 cultured in bFGF and EGF more closely mirror the phenotype and genotype of primary tumors

697 than do serum-cultured cell lines. *Cancer Cell*. May 2006;9(5):391-403.
698 doi:10.1016/j.ccr.2006.03.030

699 43. Gomez-Oliva R, Dominguez-Garcia S, Carrascal L, et al. Evolution of Experimental
700 Models in the Study of Glioblastoma: Toward Finding Efficient Treatments. *Front Oncol*.
701 2020;10:614295. doi:10.3389/fonc.2020.614295

702 44. Wanigasekara J, Cullen PJ, Bourke P, Tiwari B, Curtin JF. Advances in 3D culture
703 systems for therapeutic discovery and development in brain cancer. *Drug Discov Today*. Nov
704 1 2022;103426. doi:10.1016/j.drudis.2022.103426

705 45. Caragher S, Chalmers AJ, Gomez-Roman N. Glioblastoma's Next Top Model: Novel
706 Culture Systems for Brain Cancer Radiotherapy Research. *Cancers (Basel)*. Jan 4
707 2019;11(1)doi:10.3390/cancers11010044

708 46. Gomez-Roman N, Chong MY, Chahal SK, et al. Radiation Responses of 2D and 3D
709 Glioblastoma Cells: A Novel, 3D-specific Radioprotective Role of VEGF/Akt Signaling through
710 Functional Activation of NHEJ. *Mol Cancer Ther*. Feb 2020;19(2):575-589. doi:10.1158/1535-
711 7163.MCT-18-1320

712 47. Olubajo F, Achawal S, Greenman J. Development of a Microfluidic Culture Paradigm
713 for Ex Vivo Maintenance of Human Glioblastoma Tissue: A New Glioblastoma Model? *Transl*
714 *Oncol*. Jan 2020;13(1):1-10. doi:10.1016/j.tranon.2019.09.002

715 48. Vinel C, Rosser G, Guglielmi L, et al. Comparative epigenetic analysis of tumour
716 initiating cells and syngeneic EPSC-derived neural stem cells in glioblastoma. *Nat Commun*.
717 Oct 21 2021;12(1):6130. doi:10.1038/s41467-021-26297-6

718 49. Zwain T, Alder JE, Sabagh B, Shaw A, Burrow AJ, Singh KK. Tailoring functional
719 nanostructured lipid carriers for glioblastoma treatment with enhanced permeability through
720 in-vitro 3D BBB/BBTB models. *Mater Sci Eng C Mater Biol Appl*. Feb 2021;121:111774.
721 doi:10.1016/j.msec.2020.111774

722 50. University of Edinburgh. Glioma Cellular Genetics Resource. Accessed 22.12.2022,
723 2012. [https://www.ed.ac.uk/cancer-centre/cruk-brain-tumour-centre-of-excellence/glioma-](https://www.ed.ac.uk/cancer-centre/cruk-brain-tumour-centre-of-excellence/glioma-cellular-genetics-resource)
724 [cellular-genetics-resource](https://www.ed.ac.uk/cancer-centre/cruk-brain-tumour-centre-of-excellence/glioma-cellular-genetics-resource)

725 51. British Neuro-Oncological Society. Preclinical Models.
726 <https://www.bnos.org.uk/preclinical-models/>

727 52. Fougner V, Hasselbalch B, Lassen U, Weischenfeldt J, Poulsen HS, Urup T.
728 Implementing targeted therapies in the treatment of glioblastoma: Previous shortcomings,
729 future promises, and a multimodal strategy recommendation. *Neurooncol Adv*. Jan-Dec
730 2022;4(1):vdac157. doi:10.1093/noajnl/vdac157

731 53. GlioModel. GlioModel: A Preclinical Modelling Resource for High Grade Glioma.
732 Accessed 22.12.2022, 2022. <https://gliomodel.org.uk>

733 54. Sokolov AV, Dostdar SA, Attwood MM, et al. Brain Cancer Drug Discovery: Clinical
734 Trials, Drug Classes, Targets, and Combinatorial Therapies. *Pharmacol Rev*. Oct 2021;73(4):1-
735 32. doi:10.1124/pharmrev.121.000317

736 55. Morgan P, Brown DG, Lennard S, et al. Impact of a five-dimensional framework on
737 R&D productivity at AstraZeneca. *Nat Rev Drug Discov*. Mar 2018;17(3):167-181.
738 doi:10.1038/nrd.2017.244

739 56. Fernando K, Menon S, Jansen K, et al. Achieving end-to-end success in the clinic:
740 Pfizer's learnings on R&D productivity. *Drug Discov Today*. Mar 2022;27(3):697-704.
741 doi:10.1016/j.drudis.2021.12.010

742 57. Shimura H, Masuda S, Kimura H. Research and development productivity map:
743 visualization of industry status. *J Clin Pharm Ther*. Apr 2014;39(2):175-80.
744 doi:10.1111/jcpt.12126

745 58. Muller S, Weigelt J. Open-access public-private partnerships to enable drug discovery-
746 new approaches. *IDrugs*. Mar 2010;13(3):175-80.

747 59. Experimental Cancer Medicine Centre Network. Experimental Cancer Trial Finder
748 Accessed 23rd Aug, 2023. <https://www.ecmcnetwork.org.uk/ec-trial-finder>

749 60. Alexander BM, Ba S, Berger MS, et al. Adaptive Global Innovative Learning
750 Environment for Glioblastoma: GBM AGILE. *Clin Cancer Res*. Feb 15 2018;24(4):737-743.
751 doi:10.1158/1078-0432.CCR-17-0764

752 61. Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment
753 Practices, and Trial Designs Guidance for Industry (2020).

754 62. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for
755 newly diagnosed glioblastoma. *N Engl J Med*. Feb 20 2014;370(8):699-708.
756 doi:10.1056/NEJMoa1308573

757 63. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for
758 newly diagnosed glioblastoma. *N Engl J Med*. Feb 20 2014;370(8):709-22.
759 doi:10.1056/NEJMoa1308345

760 64. Stupp R, Hegi ME, Gorlia T, et al. Cilengitide combined with standard treatment for
761 patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC
762 EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. *Lancet*
763 *Oncol*. Sep 2014;15(10):1100-8. doi:10.1016/S1470-2045(14)70379-1

764 65. Westphal M, Heese O, Steinbach JP, et al. A randomised, open label phase III trial with
765 nimotuzumab, an anti-epidermal growth factor receptor monoclonal antibody in the
766 treatment of newly diagnosed adult glioblastoma. *Eur J Cancer*. Mar 2015;51(4):522-532.
767 doi:10.1016/j.ejca.2014.12.019

768 66. Weller M, Butowski N, Tran DD, et al. Rindopepimut with temozolomide for patients
769 with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-
770 blind, international phase 3 trial. *Lancet Oncol*. Oct 2017;18(10):1373-1385.
771 doi:10.1016/S1470-2045(17)30517-X

772 67. Stupp R, Taillibert S, Kanner A, et al. Effect of Tumor-Treating Fields Plus Maintenance
773 Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With
774 Glioblastoma: A Randomized Clinical Trial. *JAMA*. Dec 19 2017;318(23):2306-2316.
775 doi:10.1001/jama.2017.18718

776 68. Herrlinger U, Tzaridis T, Mack F, et al. Lomustine-temozolomide combination therapy
777 versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with
778 methylated MGMT promoter (CeTeG/NOA-09): a randomised, open-label, phase 3 trial.
779 *Lancet*. Feb 16 2019;393(10172):678-688. doi:10.1016/S0140-6736(18)31791-4

69. Millward CP, Armstrong TS, Barrington H, et al. Development of 'Core Outcome Sets' for Meningioma in Clinical Studies (The COSMIC Project): protocol for two systematic literature reviews, eDelphi surveys and online consensus meetings. *BMJ Open*. May 9 2022;12(5):e057384. doi:10.1136/bmjopen-2021-057384
70. Retzer A, Sivell S, Scott H, et al. Development of a core outcome set and identification of patient-reportable outcomes for primary brain tumour trials: protocol for the COBra study. *BMJ Open*. Sep 30 2022;12(9):e057712. doi:10.1136/bmjopen-2021-057712
71. Collins A, Lethborg C, Brand C, et al. The challenges and suffering of caring for people with primary malignant glioma: qualitative perspectives on improving current supportive and palliative care practices. *BMJ Support Palliat Care*. Mar 2014;4(1):68-76. doi:10.1136/bmjspcare-2012-000419
72. Piil K, Juhler M, Jakobsen J, Jarden M. Controlled rehabilitative and supportive care intervention trials in patients with high-grade gliomas and their caregivers: a systematic review. *BMJ Support Palliat Care*. Mar 2016;6(1):27-34. doi:10.1136/bmjspcare-2013-000593
73. Kurian KM, Jenkinson MD, Brennan PM, et al. Brain tumor research in the United Kingdom: current perspective and future challenges. A strategy document from the NCRI Brain Tumor CSG. *Neurooncol Pract*. Mar 2018;5(1):10-17. doi:10.1093/nop/npa022
74. Rooney AG, Hewins W, Walker A, et al. Lifestyle coaching is feasible in fatigued brain tumor patients: A phase I/feasibility, multi-center, mixed-methods randomized controlled trial. *Neuro-Oncology Practice*. 2022:npa086. doi:10.1093/nop/npa086
75. Jenkinson MD, Watts C, Marson AG, et al. TM1-1 Seizure prophylaxis in gliomas (SPRING): a phase III randomised controlled trial comparing prophylactic levetiracetam versus no prophylactic anti-epileptic drug in glioma surgery. *Journal of Neurology, Neurosurgery & Psychiatry*. 2019;90(3):e8. doi:10.1136/jnnp-2019-ABN.25