

Final results of a randomized, controlled, phase 3 trial comparing resection and post-operative stereotactic radiation versus resection and cesium-131 tile-based radiation for treatment of newly diagnosed brain metastases.

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A multicenter randomized phase III study for newly diagnosed, maximally resected glioblastoma comparing carmustine wafer implantation followed by chemoradiotherapy with temozolomide versus chemoradiotherapy alone: Japan Clinical Oncology Group study JCOG1703 (MACS study).

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Background: Three randomized phase III trials evaluated carmustine wafers (CWs) before temozolomide (TMZ) became standard therapy. To date, no randomized study has assessed CWs with standard TMZ chemoradiotherapy in newly diagnosed glioblastoma (GB). A post hoc analysis of Westphal's phase III trial, which evaluated CWs versus placebo, suggested a survival benefit with CWs in GB patients with $\geq 90\%$ resection. We conducted a randomized phase III trial to determine whether adding CWs to standard chemoradiotherapy improves overall survival (OS) in newly diagnosed GB with $\geq 90\%$ resection. **Methods:** This multicenter trial (38 institutions; JCOG1703) enrolled patients with newly diagnosed GB considered resectable at $\geq 90\%$. After intraoperative pathological confirmation of malignant glioma and $\geq 90\%$ removal, patients were randomized (1:1) to CW implantation (Arm B) or no implantation (Arm A). Arm B received intraoperative placement of up to 8 CWs. All patients received 60 Gy radiotherapy with concomitant daily TMZ followed by 12 cycles of maintenance TMZ. The primary endpoint was OS; secondary endpoints included progression-free survival (PFS), loco-regional PFS (LPFS), and adverse events. DNA methylation array analysis and molecular testing included MGMT promoter methylation and copy number profiling. **Results:** Among 234 registered patients, 221 (Arm A, $n=110$; Arm B, $n=111$) were randomized between June 2019 and November 2022. Baseline characteristics were well balanced. Median OS for all randomized patients was 26.5 months (1-year 86.4%, 2-year 54.3%, 5-year 16.6%), with no significant difference between Arm A and B (21.7 vs 27.7 months; hazard ratios (HR) 0.907, 95% confidence interval (CI) 0.691–1.192; one-sided $p=0.269$ by the stratified log-rank test). Median PFS was 9.8 months (1-year 43.4%, 2-year 16.3%), also without significant difference (9.5 vs 10.4 months; HR 0.867, 95% CI 0.658–1.141). Median LPFS was 11.6 months (1-year 48.4%, 2-year 25.1%), with no difference between arms (10.6 vs 12.7 months; HR 0.886, 95% CI 0.669–1.173). MGMT promoter methylation was a significant favorable factor for OS, PFS, and LPFS. Early postoperative complications and adverse events were comparable between groups, and no treatment-related deaths occurred. **Conclusions:** CW implantation added to standard TMZ chemoradiotherapy did not significantly improve OS in newly diagnosed GB after $\geq 90\%$ resection. Based on these findings, CW implantation does not provide significant therapeutic or survival benefit when standard TMZ chemoradiotherapy is feasible in this population. Clinical trial information: jRCT1031190035. Research Sponsor: Japan Agency for Medical Research and Development; 19ck0106515; 21ck0106515; 24ck0106763.

Connectome-sparing stereotactic radiosurgery: Results from the phase II COG-SRS trial.

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Background: Cognitive decline remains common after radiosurgery. The cognition-sparing stereotactic radiosurgery trial (COG-SRS, NCT04343157) evaluated a novel connectome-sparing SRS strategy leveraging advanced imaging to autosegment the cognitive connectome for individualized functional sparing. **Methods:** COG-SRS is a prospective, single-institution, phase II trial that enrolled adults ($KPS \geq 70$) treated with SRS for benign or malignant intracranial lesions from 06/2018-10/2025. Connectome structures (10 discrete eloquent bilateral white matter tracts [WMTs], corpus callosum, and hippocampi [HC]) were auto-segmented from pretreatment diffusion tensor imaging and structural MRI and assigned evidence-based dose constraints (single fraction D_{max} WMT=12Gy, HC=8.4Gy, with 3-/5-fraction equivalent doses) during SRS planning. Neuropsychological testing assessed cognitive domains of memory, language, executive function, attention/processing speed, and fine motor control at baseline and 3 months post-SRS. Outcomes were summarized using normed T scores and analyzed with mixed effects models adjusting for baseline score and prespecified clinical covariates. In the brain metastases cohort, cognitive performance was also compared with historical controls treated with standard brain SRS on Alliance N0574/N107C using domain Z scores and baseline adjusted mixed effects models. Questionnaires assessed mood/QOL, and disease time to event endpoints were estimated by Kaplan Meier. **Results:** Ninety-two patients enrolled (mean age 57.8 years), including 82 (89%) with brain metastases. All plans met standard target coverage and organ-at-risk constraints while optimizing dose to the cognitive connectome, with 76% meeting predefined constraints for all 23 connectome structures. At 3 months, 74% of patients demonstrated stable-to-improved performance across all 5 cognitive domains, with no significant mean decline in any domain. Mean performance improved in executive function (+4.30 T; $p=0.043$) and language (+4.91 T; $p=0.011$). Compared with historical controls, COG-SRS demonstrated superior 3 month cognitive outcomes (global composite Z difference +0.38; $p=0.001$), with the most pronounced domain-level benefit in executive function (+0.71; $p=0.009$) and language (+0.35; $p=0.010$). Mood and QOL remained stable. Among patients with brain metastases (median followup 35.6 months), 1 year local control was 98.5%, freedom from distant intracranial failure 57.4%, and overall survival 66.7%. **Conclusions:** Connectome-sparing brain SRS is feasible, leveraging advanced MRI-based autosegmentation of patient-specific cognitive networks, and is associated with preserved early cognition at the cohort level with superior 3 month cognitive outcomes versus historical controls. Cognitive benefits were achieved without compromising oncologic control, supporting prospective randomized study. Clinical trial information: NCT04343157. Research Sponsor: National Institutes of Health (NIH), National Cancer Institute (NCI); R01 CA238783; National Institutes of Health (NIH), National Cancer Institute (NCI); 1R01CA289833-01.

Neoadjuvant fractionated stereotactic radiotherapy followed by surgical resection for brain metastases: A multicenter, single arm phase II trial (NEO-TACTICS).

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Background: Surgical resection followed by adjuvant radiotherapy for brain metastases (BM) is associated with unresolved challenges, including local recurrence (LR), leptomeningeal dissemination (LMD), radiation necrosis (RN), and cognitive decline. Preoperative stereotactic radiosurgery followed by surgical resection has been proposed as a novel strategy to address these limitations. This phase II trial evaluated the efficacy and safety of neoadjuvant fractionated stereotactic radiotherapy (FSRT) followed by surgical resection for BM. **Methods:** Patients with one index brain metastasis requiring surgical resection (2–5cm diameter) and up to three non-index metastases not requiring resection (< 2cm) were enrolled across 14 centers. All patients received neoadjuvant FSRT (30–35 Gy in 5 fraction) targeting the index lesion, followed by surgical resection. The primary endpoint was 6-month cumulative incidence of LR at the surgical site. Secondary endpoints included LMD, LR at 12 months, RN, distant brain failure (DBF), overall survival (OS), intracranial progression-free survival (IC-PFS), neurocognitive outcomes, and treatment-related adverse events. **Results:** Between June 2022 and August 2024, we enrolled 57 patients with 53 evaluable for response. The median age was 68 years (range 34–79). The median maximum diameter was 3.2 cm (range 2.0–4.9). The median follow-up duration was 11.9 months (range 1.3–14.7). The 6-month cumulative incidence of surgical site LR was 4.3% (95% CI: 0–10.1) (80%CI : 0.4–8.1), and 4.0% (95%CI: 0–9.4) using competing risk analysis. LMD was not observed at either 6, 12 months. The 12-month cumulative incidence of LR was 16.4% (95% CI: 6.0–26.8). Symptomatic RN ($\geq$ Gr 2) was not observed at either 6, 12 months, and asymptomatic RN occurred in 5.9% at 6 months and 8.0% at 12 months. DBF rates were 14.0% (95% CI: 4.4–23.6) at 6 months and 18.1% (95% CI: 7.4–28.8) at 12 months. Median OS rate was 86.3% (95%CI: 77.3–96.3) at 6 months, and 76.5% (95%CI: 65.7–89) at 12 months. IC-PFS rates were 72.5% (95% CI: 61.2–85.9) at 6 months and 64.4% (95% CI: 52.5–79.1) at 12 months. Neurocognitive function was largely preserved, with Mini-Mental State Examination (MMSE) decline $\geq$ 1 point observed in 15.4% at 6 months and 9.6% at 12 months, and decline $\geq$ 3 points in $\leq$ 4% at both time points. Adverse events from irradiation to surgery were acceptable (grade $\geq$ 2: 10.5%; grade $\geq$ 3: 5.3% (CTCAE version 5.0)). **Conclusions:** Neoadjuvant FSRT followed by surgical resection demonstrated excellent early local control, complete suppression of LMD, acceptable toxicity, and favorable cognitive preservation. This approach represents a promising alternative to postoperative FSRT for resectable brain metastases and warrants further comparative investigation. Clinical trial information: jRCT s042220014. Research Sponsor: ACCURAY.

MAGMA: Multi-arm glioblastoma Australasia phase 3 trial.

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Background: MAGMA (ACTRN12620000048987; COGNO cooperative trials group) is a prospective, open-label, partial factorial randomized platform trial with optional randomization, aiming to improve treatments for glioblastoma (GBM). Two initial hypotheses were tested: Question 1 (Q1), 'early' daily temozolomide (TMZ) as soon as possible postop, pre-radiotherapy (RT); and Question 2 (Q2), 'extended' adjuvant TMZ beyond 6 cycles. Prior phase 2 studies suggest longer survival with early TMZ and inconsistent outcomes with extended adjuvant TMZ. MAGMA used baseline randomization with molecular stratification aiming for robust randomized evidence. **Methods:** Participants (pts) with newly diagnosed GBM (CNS WHO 2016) could be randomized to each question, stratified by extent of resection and IDH status (Q1 and Q2) and MGMT methylation (Q2 only). For Q1, pts were randomized to daily TMZ (75 mg/m²) initiated as soon as possible after surgery followed by standard RT-TMZ (either 15 or 30 fractions), or RT-TMZ alone. For Q2, pts were randomized prior to adjuvant TMZ, to stop after 6 cycles or continue until progression. Primary outcome was overall survival (OS) from initial surgery. Secondary outcomes included progression-free survival (PFS), time to next treatment, OS from each randomization, clinically significant toxicity and health-related quality of life. **Results:** From September 2020 to July 2023, 347 pts consented across 28 Australian sites including 6 regional sites. Median follow-up was 40 months; final data cutoff was 31 July 2025. Mean age was 60 years (range 21–85), 60% were male, 92% IDH-wildtype, 42% MGMT-methylated, 56% had gross total resection and 13% biopsy-only. For Q1 (n=259), pts randomized to early TMZ (n=131) started TMZ at median 21 days post-surgery with mean exposure 13 days. Concurrent TMZ exposure, time to starting RT (median 34 vs 33 days), RT completion and toxicity (G3+ 34% vs 31%) were similar between arms. Median OS (months; 95% CI) was 16 (14–20) with early TMZ vs 20 (17–22) for control, HR 1.18 (0.89–1.56), p=0.24. Median PFS was 8 (7–9) vs 9 (7–12), HR 1.15 (0.88–1.52), p=0.31. For Q2 (n=291), among pts randomized to extended adjuvant TMZ (n=146), only 42% remained progression-free through 6 cycles and received more than 6 adjuvant TMZ cycles. Toxicity was similar between arms (G3+ 34% vs 31%). Median OS was 20 months (17–22) with extended adjuvant TMZ vs 18 (15–20) for control, HR 0.82 (0.63–1.06), p=0.13; after multivariable analysis, HR 0.73 (0.56–0.95). Median PFS was 9 (8–9) vs 9 (7–10), HR 0.88 (0.69–1.13), p=0.32. **Conclusions:** Early TMZ does not improve OS in pts with newly diagnosed GBM. Extended adjuvant TMZ beyond 6 cycles was safe, with insufficient evidence of improved OS in the primary analysis, although moderate effects remain plausible. Notably, many pts had progression before completing 6 cycles. Collaboration enables large-scale, pragmatic cancer trials across diverse healthcare settings in Australia. Clinical trial information: ACTRN12620000048987. Research Sponsor: Medical Research Future Fund (MRFF); 2018/MRF1170193.

Phase 1/2a study of concomitant radiotherapy with olaparib and temozolomide in unresectable high-grade glioma patients: Final results from the phase 2a step (OLA-TMZ-RTE-01).

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Background: Although the Stupp protocol (radiotherapy + temozolomide (TMZ)) remains the cornerstone of glioblastoma (GBM) first line treatment after surgery (resection or biopsy), the prognosis is still poor. PARP inhibitors, such as olaparib, may enhance the efficacy of radiotherapy and TMZ by amplifying their cytotoxic effects. We implemented a phase 1/2 trial to assess safety and efficacy of olaparib combined with TMZ concomitant with intensity modulated radiotherapy (IMRT) as a first line treatment in GBM patients (pts) following biopsy or subtotal resection. The phase 1 conducted in 30 pts concluded the recommended phase 2 dose (RP2D) of olaparib was 100 mg Q12H Day (D) 1–3, in concomitant with the Stupp protocol. We herein report results of the phase 2a. **Methods:** Pts were treated with adjuvant IMRT (60 Gy/30 fractions/6 wks), with concurrent daily oral TMZ (75 mg/m²). For the maintenance period (MT) from 4 wks after IMRT, pts received TMZ (150 mg/m², D 1–5 every 28 days, for 6 cycles). Oral olaparib was started at the RP2D the same day as IMRT, concurrently with the Stupp protocol and continued up to disease progression or unacceptable toxicity. The trial was conducted according to a two-step Case and Morgan design and required 55 assessable pts (37 in interim analysis), to assess the 12-month (mo) overall survival (OS) rate expected to be higher than 57%. Final Z-statistic > 1.235 will confirm efficacy. All pts who received olaparib at RP2D were included in the analysis, including pts of the phase 1 step. **Results:** From 2020 to 2024, 68 pts were enrolled and treated in the phase 2a: 41 (60%) men, median age 59 yrs [range 20–70]. 67 pts (98%) had GBM and 1 (2%) IDH mutated anaplastic astrocytoma. Biopsy-only was performed for 27 pts (40%). ECOG performance status 0 for 34 pts (51%), 1 for 28 pts (42%) and 2 for 5 (7%). 11 pts (16%) stopped the study before MT, including 4 for grade 3–4 hematological toxicity. Among the 57 pts who began the MT, 5 stopped the treatment for hematological toxicity. 3 pts remain on treatment. Interim analysis conducted in March 2024 in 41 patients, with median follow-up 7.6 mo, led pursuing the study, with a 12-mo OS rate of 72.9% [95%CI: 56.7–93.9]. At final analysis, after median follow-up of 17.2 mo, 48 deaths (71%) were observed. Median OS was 18.4 mo and 12-mo OS rate of 69.1% [95%CI: 59–81] (H0 rejection according to Z-statistic=1.29). Among hematological toxicities of interest, thrombocytopenia grade ≥ 3 was observed in 5 pts, neutropenia grade 4 in 4 pts, febrile neutropenia grade ≥ 3 in 1 pt and anemia grade ≥ 3 in 4 pts. One toxic death was observed (febrile aplasia). **Conclusions:** Intermittent olaparib (100 mg Q12H D1–3) combined with the Stupp protocol appears to be beneficial to improve survival of poor prognosis nonresected/partially resected GBM pts, with a safety profile quite similar to that of the standard chemoradiotherapy. Clinical trial information: NCT03212742. Research Sponsor: French Cancer Institute and French Health Ministry; Astra-Zeneca.

A personalized neoantigen vaccine to reprogram the immune landscape of glioblastoma.

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Background: Glioblastoma (GBM) remains uniformly lethal despite standard therapy. An immunosuppressive tumor microenvironment (TME) and limited T cell infiltration pose major barriers to immunotherapy. Personalized neoantigen vaccines offer a strategy to prime tumor-specific T cell responses by targeting patient-specific mutations, driving effector cells into the CNS. Here, we report results from a phase I trial of a personalized neoantigen peptide vaccine combined with pembrolizumab in newly diagnosed GBM. **Methods:** Patients with newly diagnosed GBM who were not on dexamethasone following gross total resection were enrolled across four cohorts. Up to 20 synthetic long peptides targeting personal neoantigens were selected per patient, and admixed with the adjuvant poly-ICLC (NeoVax). Following radiotherapy, NeoVax was administered subcutaneously as five priming doses followed by two booster doses. *MGMT*-unmethylated patients (Cohorts 1A-C) received NeoVax plus pembrolizumab without temozolomide (TMZ) and differed by time of pembrolizumab initiation relative to NeoVax priming; *MGMT*-methylated patients (Cohort 1D) received standard TMZ and pembrolizumab was initiated after NeoVax priming. Immunogenicity was assessed by *ex vivo* and *in vitro* IFN- γ ELISpot assays. Single-nucleus/single-cell RNA sequencing and TCR sequencing (snRNA-seq/scTCR-seq) was performed on paired tumor specimens. **Results:** Of 39 enrolled patients, 37 initiated NeoVax including 35 who completed priming and 2 with ongoing priming. Treatment was well-tolerated with no serious AEs. Median overall survival was 36.9 months for *MGMT*-methylated patients and 19.0 months for *MGMT*-unmethylated patients, compared to 25.3 and 16.7 months for propensity score-matched historical controls, respectively. *Ex vivo* and *in vitro* neoantigen-specific T cell responses were detected comparably across all cohorts and overall in 65% and 97% of vaccinated patients, respectively. Among all patients, *ex vivo* immune responders demonstrated improved overall survival compared to non-responders (HR 0.26, 95% CI 0.09-0.77, $P = 0.015$). Vaccine-reactive clonotypes, defined by *in vitro* expansion to vaccine peptides, were identified in post-vaccination tumors. snRNA-seq/scTCR-seq revealed increased intratumoral vaccine-specific T effector populations following vaccination. **Conclusions:** NeoVax generates durable T cell responses that traffic to GBM tumors, with circulating responses associated with improved survival. Ongoing studies are evaluating peripheral clonotype dynamics, remodeling of malignant cell states and the TME, and the spatial distribution of vaccine-reactive clonotypes, which may guide future combinatorial strategies in GBM. Clinical trial information: NCT02287428. Research Sponsor: The Ben & Catherine Ivy Foundation; Accelerate Brain Cancer Cure; Merck Sharp & Dohme LLC; U.S. National Institutes of Health; 5P01CA236749; U.S. National Institutes of Health.

Efficacy and safety of asandeutertinib versus osimertinib as first-line treatment in EGFR-mutated NSCLC patients with brain metastases: Interim analysis of an open-label, multicenter, randomized, pivotal phase II study (ESAONA).

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Correlation of ten-year survival with cell-free DNA methylation of melanoma patients with asymptomatic brain metastases treated with nivolumab plus ipilimumab: The multicenter phase III NIBIT-M2 trial.

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Background: The NIBIT Foundation-sponsored phase III NIBIT-M2 study showed a 41% 7-y OS of melanoma patients (pts) with asymptomatic brain metastases (BM) treated with ipilimumab (I) plus nivolumab (N) (I+N) (*Di Giacomo AM, CCR 2021 and EJC 2024*). Despite the significant efficacy of I+N therapy in this pts population, no biomarkers predictive of response have been identified yet also due to the accessibility of BM. We here report the 10-y survival and its correlation with cell-free (cf)DNA analyses on serial plasma samples collected from pts enrolled in the NIBIT-M2 study. **Methods:** The NIBIT-M2 study recruited melanoma pts with active, untreated, asymptomatic BM from 9 Italian Centers, randomized (1:1:1) to receive fotemustine (F) (Arm A), I+F (Arm B), or I+N (Arm C). Primary endpoint was OS. Exploratory analyses were conducted on cfDNA plasma samples collected at baseline and week (W) 12 on therapy. Tumor fraction (TF) was estimated from low pass WGS using IchorCNA. Tumor-specific methylation Score (T-meth Score) was computed as the ratio between the coverage over methylated regions analyzed by cf-methylated DNA immunoprecipitation and high-throughput sequencing (cfMedIP-seq) and melanoma-specific methylated regions previously identified in the TCGA melanoma cohort. **Results:** From Jan 2013 to Sept 2018, 80 pts were enrolled: 76 received F (23), I+F (26), or I+N (27). As of December 1, 2025, with a median follow-up of 125 months (mo), median OS was 8.5 (95% CI: 4.8-12.2), 8.2 (95% CI: 2.1-14.3) and 29.2 (95% CI: 0-73.5) mo for Arm A, B, and C, respectively. The 10-y OS rate was 13.0% (95% CI: 0-26.7) in Arm A, 7.7% (95% CI: 0-17.9) in Arm B, and 31.2% (95% CI: 13.0-49.4) in Arm C. The 10-y melanoma specific survival was 13.0% (95% CI: 0-26.7), 7.7% (95% CI: 0-17.9), and 35.1% (95% CI: 16.3-53.9) in Arm A, B and C, respectively. Patients were stratified at baseline according to the median values of TF (n=57; median 0.022) and of T-meth Score (n=53; median 0.096): a significantly higher median OS was observed in pts with TF (22.3 vs 8.2 mo; p=0.033) and T-meth Score (26.3 vs 7.9 mo; p=0.002) below their median values. Of note, low TF and T-meth Score were enriched at baseline in pts from Arm C. Additionally, a decrease in TF (n=29) and T-meth Score (n=24) was observed at W12 in pts with an OS above the median (26.3 mo for TF and 24.0 mo for T-meth Score). **Conclusions:** The 10-y results of the NIBIT-M2 study, with the longest follow-up available to date in melanoma pts with asymptomatic BM treated with I+N, continue to show persistent long-term therapeutic efficacy of the combination. Plasma-derived TF and T-meth Score may predict long-term survival of melanoma pts with asymptomatic BM treated with I+N. Clinical trial information: NCT02460068. Research Sponsor: FONDAZIONE AIRC; 21073; Bristol Myers Squibb; NA.

SPECTRUM: Phase II study of tislelizumab plus pemetrexed in patients with relapsed or refractory (R/R) primary diffuse large B-cell lymphoma (DLBCL) of the central nervous system (CNS)—The Korean Cancer Study Group LY22-07.

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Background: Primary DLBCL of the CNS is a rare extranodal lymphoma confined to the CNS. Despite standard high-dose methotrexate (HD-MTX)-based induction therapy, approximately 25% of patients (pts) relapse after an initial response, and effective salvage options are limited with reported objective response rate (ORR) generally <30% and median progression-free survival (PFS) <3 months. The SPECTRUM trial evaluated efficacy and safety of tislelizumab plus pemetrexed in pts with R/R primary DLBCL of the CNS (NCT05253118). **Methods:** SPECTRUM is a phase II, multicenter, open-label study conducted in South Korea. Pts with histologically confirmed R/R primary DLBCL of the CNS after HD-MTX-based therapy were eligible. Tislelizumab (200 mg) plus pemetrexed (500 mg/m²) was administered intravenously every 3 weeks until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed ORR per IPCG response criteria. Secondary endpoints included PFS, duration of response (DoR), overall survival (OS), and safety. Exploratory analyses assessed baseline CSF and plasma MYD88 L265P mutations using droplet digital PCR and genetic subtypes based on LymphGen classification. **Results:** As of December 16, 2025, 29 pts were enrolled. Median age was 59 years (range, 41–86), 17 (58.6%) were male, and 25 (86.2%) had prior rituximab exposure. Median follow-up was 30.4 months (95% confidence interval [CI], 16.8–not reached [NR]), with a median of 6 treatment cycles (range, 1–55). Among evaluable pts, the ORR was 71.4% (20/28), with complete response (CR) rate of 50.0% (14/28). Median DoR was 14.5 months (95% CI, 2.8–NR). Median PFS and OS were 6.8 (95% CI, 2.1–27.6) and 27.8 months (95% CI, 7.4–NR), respectively. Treatment-emergent adverse events (TEAEs) of any grade occurred in 19 pts (65.5%), most commonly skin rash (51.7%). Grade ≥3 TEAEs occurred in 10 pts (34.5%), including one grade 5 event. Six pts discontinued treatment due to treatment-related AEs, all attributable to pemetrexed. Immune-related AEs occurred in 5 pts (17.2%). Most pts were MCD subtype (84.6% [22/26]), with MYD88 L265P mutations detected in 61.5% (16/26). At baseline, MYD88 L265P detection was higher in CSF than plasma cell-free DNA (cfDNA) (85.0% [17/20] vs 20.0% [4/20]). In one pt with extra-CNS relapse harboring MYD88 L265P mutation and *PIM1-CD274* fusion, MYD88 L265P became undetectable at Weeks 6 and 12, concordant with metabolic CR on PET/CT. **Conclusions:** Tislelizumab plus pemetrexed met the primary endpoint and demonstrated encouraging outcomes (ORR 71.4% [CR 50.0%]; median PFS and DoR 6.8 and 14.5 months) with manageable safety profiles in pts with R/R primary DLBCL of the CNS. Clinical trial information: NCT05253118. Research Sponsor: BeOne Medicines, Samyang Biopharm Corporation.

A global, randomized, double-blinded, phase 3 trial of vorasidenib vs placebo in patients with grade 2 glioma with an *IDH1/2* mutation (INDIGO): Updated efficacy and safety.

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Background: Grade 2 gliomas with isocitrate dehydrogenase 1/2 mutations (mIDH1/2) are diffuse, slowly progressive, malignant brain tumors with a poor long-term prognosis. In the Phase 3 INDIGO trial (NCT04164901) of patients (pts) with grade 2 mIDH1/2 glioma, vorasidenib (VOR), an oral, brain-penetrant, dual inhibitor of mIDH1/2, demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint, progression-free survival (PFS) per blinded independent review committee (BIRC), and key secondary endpoint, time to next intervention (TTNI), vs placebo (PBO) at the preplanned interim analysis (data cut-off [DCO]: September 6, 2022). An additional 6 months of data up to study unblinding, March 7, 2023, showed that median PFS was not reached (95% confidence interval [CI]: 22.1 mos, not estimable [NE]) with VOR vs 11.4 mos (95% CI: 11.1, 13.9) with PBO, and median TTNI was NE (95% CI: NE, NE) with VOR vs 20.1 mos (95% CI: 17.5, 27.1) with PBO. Here, we present updated efficacy and safety results as of January 17, 2025, from pts randomized to VOR. **Methods:** Key eligibility criteria included residual/recurrent grade 2 mIDH1/2 oligodendroglioma or astrocytoma after surgery only; aged ≥ 12 years; Karnofsky performance score ≥ 80 ; measurable non-enhancing disease; surgery as only prior treatment; no immediate need of chemoradiotherapy (CT/RT). Pts were randomized 1:1 to VOR 40 mg daily in 28-day cycles or PBO. After study unblinding, pts receiving PBO were permitted to cross over to VOR. Primary endpoint: radiographic PFS per BIRC. Key secondary endpoint: TTNI. **Results:** 331 pts were randomized: 168 to VOR and 163 to PBO (median age: 40.0 years [range: 16–71]; oligodendroglioma: 172; astrocytoma: 159). As of January 17, 2025, 98/168 (58.3%) pts remained on VOR, and median follow-up was 41.6 mos (95% CI: 40.5, 42.7). Median PFS per investigator (INV) in pts randomized to VOR was 49.9 mos (95% CI: 39.6, NE), and median TTNI was NE (95% CI: 52.0 mos, NE). At 42 mos, 59.2% (95% CI: 49.9, 67.4) of pts were progression-free and 75.1% (95% CI: 67.4, 81.2) were not in need of CT/RT or surgery. Objective response rate per INV was 31.5% (95% CI: 24.6, 39.2). Median overall survival was not reached. PFS and overall response per BIRC will be presented. The safety profile of VOR was consistent with previous reports. No new safety signals were observed. **Conclusions:** In the randomized, Phase 3 trial of a targeted therapy in grade 2 mIDH1/2 glioma, over 3 years of follow-up in pts randomized to VOR support the robustness of PFS and TTNI results and confirm a durable and sustained treatment benefit with VOR. VOR is now approved in over 40 countries as a monotherapy for pts with grade 2 mIDH1/2 glioma following surgery. Clinical trial information: NCT04164901. Research Sponsor: Servier Pharmaceuticals.

Outcomes of a feasibility and safety trial of tile-based radiation therapy with cesium-131 followed by external beam radiation therapy with concurrent and adjuvant temozolomide in patients with newly diagnosed glioblastoma (NCT05342883).

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Background: Standard of care (SOC) of Glioblastoma (GBM) includes maximal safe resection followed by external beam radiation therapy (EBRT) with concomitant temozolomide (TMZ). This typically begins 4–6 weeks after surgery, during which rapid early progression (REP) occurs in ~50% of patients and is associated with worse survival, especially in unmethylated GBM (median OS ~13 months as per BN007). SOC treatment in BN007 showed ~38% $\geq$ grade 3 treatment-related adverse events (TRAEs). GammaTile (GT Medical Technologies, Inc., Tempe, AZ), a tile-based radiation therapy (TBRT) with cesium-131 sources, immediately initiates radiation at resection, eliminating the 4–6-week delay. **Methods:** This is a prospective, single arm, open-label feasibility study across 15 US centers with a primary aim of assessing the safety and feasibility of combining resection + TBRT with an abbreviated course of EBRT with concurrent and adjuvant TMZ for newly diagnosed molecular GBM. Eligible patients were $\geq$ 18 years old; only patients with IDH-wildtype were included in survival analysis. MGMT and IDH underwent central lab review. Feasibility was defined as percent of patients who started EBRT+TMZ between 21–35 days post-surgery. Safety was assessed by incidence of $\geq$ grade 3 TRAEs. REP was centrally reviewed. Additional aims included PFS and OS estimated using Kaplan-Meier. A planned sample size of 61 was chosen to ensure feasibility could be estimated with a $\pm$ 10% degree of precision. Results are presented based on the modified intent to treat (mITT) population (enrolled patients who had surgery and confirmed GBM). **Results:** From 8/2022–8/2025, 70 patients were enrolled and had surgery; 67 of whom had confirmed GBM. Table 1 presents baseline characteristics. Median follow-up was 12.4 months. 93% started EBRT+TMZ; 74% started 21–35 days post-surgery. The median (range) of days from surgery to EBRT+TMZ was 29 (23–70) days. There were no delays due to EBRT planning. 39% of patients experienced a $\geq$ grade 3 TRAE: 22% of patients were related to surgery only, 18% to radiation only, and 13% to surgery and radiation. 6.0% of patients showed REP. Median OS for patients with unmethylated MGMT was 16.5 months vs. 28.0 months for patients with methylated MGMT. The median PFS for patients with unmethylated MGMT was 9.3 months vs. not yet met for patients with methylated MGMT. **Conclusions:** Feasibility and safety are in line with SOC. REP had a notable reduction compared to literature. OS is encouraging. These data provide the basis for a phase 3 randomized trial (NCT07195591). Clinical trial information: NCT05342883. Research Sponsor: GT Medical Technologies, Inc.

Baseline characteristics.

Parameter	Detail
n	67
Age, median	66
Male:Female, n	42:25
Ethnicity (Non-Hispanic), n	61
Race (White), n	56
EOR – GTR: not GTR, %	66:34
IDH-wildtype:mutated, n	66:1
MGMT promoter methylated:unmethylated, n	28:39

First-in-human study of AAV6-NeuroD1 trans-differentiation therapy in recurrent malignant glioma.

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Background: Recurrent glioblastoma (GBM) has a median survival of less than 9 months. NeuroD1 is a neural transcriptional factor that can reprogram both glial cells and glioma cells into neuron-like cells, suppressing the proliferation of glioma cells and inducing cell death, extending the life span of animal models carrying glioblastoma. Therefore, scAAV6-NeuroD1 (NXL-004), a self-complementary adeno-associated virus 6 vector delivering NeuroD1, was developed to initiate a first-in-human study in patients with recurrent malignant glioma (ChiCTR2400080362). **Methods:** This is a single arm, open-label, dose-escalation study. The primary endpoint was safety, and the secondary endpoint was preliminary efficacy. Enrolled patients must have pathologically confirmed recurrent malignant glioma after standard therapy including surgery and chemoradiotherapy. NXL-004 was delivered intracavitary post-resection or intratumorally post-biopsy during surgery. Three dose levels (from 4.0×10^{12} vg to 4.0×10^{13} vg) were evaluated, using an accelerated dose escalation design. Up to two additional doses were allowed via an Ommaya reservoir at 2~4-week intervals after surgery. **Results:** 11 patients (median age 48.0, 81.8% male) were enrolled between 3/2024 and 6/2025. All patients had recurrent WHO grade 4 astrocytoma (10/11 IDH wild, 6/11 MGMT-unmethylated). Ten patients received repeat tumor resection plus intracavitary injection of NXL-004 (1 at low-dose, 3 at medium-dose, and 6 at high-dose), and one received biopsy plus intra-tumoral injection (low dose). All patients were included in the safety and efficacy analysis. No drug-related serious adverse event (SAE) or dose-limiting toxicities (DLT) was observed. All AEs related to NXL-004 were grade 1–2 (fever: 8/11; rash: 1/11; seizure: 1/11). Two grade 3 AEs (hemiplegia, meningitis) were reported but considered unrelated to the drug. Per RANO 2.0 criteria, the best overall response included 1 complete response (CR) and 5 stable disease (SD), yielding a disease control rate (DCR) of 54.5% (6/11). The median overall survival for all treated patients was 13.2 ± 2.0 months (95% CI: 9.3–17.1) from the first dose and 25.2 ± 1.2 months (95% CI: 23.0–27.5) from initial diagnosis. The first enrolled patient survived >18 months after dose. In the high-dose group, a higher DCR of 66.7% (4/6) was observed, with one patient achieving CR and one with SD surviving without progression >6 months (9 and 7 months, respectively, both ongoing). At a median follow-up of 9.0 months for this group, 5 patients were still alive, with 1 patient deceased (OS: 13.2 months). **Conclusions:** To our knowledge, this is the first clinical evidence of in vivo AAV-based trans-differentiation gene therapy for cancer treatment. NXL-004 showed favorable safety and encouraging efficacy, indicating that AAV-based cell reprogramming approach may represent a new modality for the treatment of glioma. Clinical trial information: ChiCTR2400080362. Research Sponsor: Suzhou Science and Technology Plan Project No. SZM2023019; NeuExcell Therapeutics.

Updated overall survival, safety, and neurologic function outcomes from a phase 1 trial of bivalent chimeric antigen receptor (CAR) T cell therapy in recurrent glioblastoma (GBM).

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Background: We previously reported the safety, bioactivity, and preliminary efficacy of bivalent CAR T cells targeting EGFR and IL13R α 2 in 18 patients with recurrent GBM (Bagley, et. al, *Nat Med* 2025). Given that median follow-up time was only 8.1 months at the time of the data cut-off for that publication, we now report updated overall survival (OS) and safety data with longer follow-up time, as well as neurologic function outcomes. **Methods:** Eighteen patients with recurrent EGFR-amplified GBM were enrolled using a 3+3 design (dose levels: 5.0×10^6 , 1.0×10^7 , and 2.5×10^7 cells). Patients received a single intracerebroventricular (ICV) dose of CART-EGFR-IL13R α 2 cells. OS was defined as the time from the date of initial study treatment to the date of death from any cause, or censored at the last date of contact if the patient was not known to have died at the date of analysis cut-off (January 16, 2026). To capture changes in neurologic function over the course of the trial, patients were assessed prospectively using the Neurologic Assessment in Neuro-Oncology (NANO) scale. NANO is an objective clinician-reported outcome of neurologic function scored on nine domains, with a higher score indicating worse neurologic function. NANO scores were assessed at baseline prior to CART (day 0), on days 1, 4, 7, 10, 14, 21, and at the 1-month and 2-month visits post-CART. **Results:** With median follow-up time of 18.5 months, median OS was 12.0 months (95% confidence interval, 7.4 – 23.2 months) with 3 patients surviving greater than 18 months. Other than one patient with prolonged grade 1 neurotoxicity as previously described, no prolonged, late-onset, or unexpected toxicities were observed within this longer follow-up time, including no evidence of on-target off-tumor toxicity or secondary cancers. On day 1 post infusion, an increase in NANO scores was observed (mean increase in NANO score from baseline of 1.9; $p=0.09$), which resolved to baseline by day 4. Patient NANO scores were unchanged from baseline at one month (mean change 0.41; $p=0.998$) and two months (mean change 0.54; $p=0.992$) post infusion. Those who underwent retreatment with a second dose of CAR-T cells at the time of tumor progression ($n=7$) did not experience an increase in NANO score on day 1 (mean change 0.33, $p=0.99$), despite having a significant increase on day 1 following the first infusion (mean change 2.9, $p=0.008$). **Conclusions:** With over 18 months of median follow-up time, ICV delivery of CART-EGFR-IL13R α 2 cells in patients with recurrent GBM has not demonstrated long-term or delayed toxicities and is associated with promising OS outcomes that warrant continued clinical development. Neurologic function worsens immediately following infusion but recovers to pre-treatment baseline by one month following CAR T cell infusion. Clinical trial information: NCT05168423. Research Sponsor: Kite.

Butaselen combined with radiotherapy for newly diagnosed H3K27M-mutant spinal diffuse midline glioma: A single-arm phase Ib trial.

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Background: Patients with H3K27M-mutant spinal diffuse midline glioma (sDMG) have a median overall survival (OS) of approximately 13 months and the medical interventions remain limited. Radiation induced senescence (RIS) is a major cause of radiotherapy resistance and tumor recurrence in H3K27M-mutant sDMG. In pre-clinical study, we observe that thioredoxin reductase 1 (TrxR1) protects senescence sDMG cells from oxidative damage caused by radiation, and novel TrxR1 inhibitor Butaselen dramatically induces apoptosis of sDMG cells. Therefore, Butaselen combined radiotherapy is a new strategy to prolong the OS and progression-free survival (PFS) for newly diagnosed H3K27M-mutant sDMG patients. **Methods:** Patients age 18–70 years with newly diagnosed H3K27M-mutant sDMG were eligible for this phase Ib trial (ChiCTR2600116732). All subjects received fixed radiation dose at 45Gy/1.8f/25d. Dose-escalation of Butaselen was performed in phase Ib trial and 9 subjects were enrolled in three dose levels (3+3 design: DL1: 450mg, oral, bid; DL2: 600mg, oral, bid; DL3: 750mg, oral, bid). Butaselen was orally administered in combination with radiotherapy for first 5 weeks, and then administered alone until tumor progression occurs or death. Follow-up visits were conducted at Q8W during 0–6 months and Q12W afterwards. The primary outcome was the safety of the Butaselen, as determined on the basis of adverse events (AEs) and serious adverse events (SAEs). The secondary outcomes were the 12-month OS/PFS rate, OS, PFS, objective response rate (ORR, RANO 2.0 criteria), and objective neurological function scale. **Results:** Between Apr 18, 2024 and May 21, 2025, 9 eligible subjects were enrolled. 9 subjects (age 26–57 years) received Butaselen therapy with no report of severe adverse event (SAE) or dose-limiting toxicity. As a result, 6-month and 12-month PFS rate (PFS%) was 100% and 88.9% (8/9), respectively, while both 6-month and 12-month OS rate (OS%) reached 100%. The longest PFS has exceed 22 months. 1 subject was died due to disease progress (OS=14.7 month; PFS=6.9 month), 1 subject experienced second operate resecting after disease progress (PFS=12.9 month), and the remaining 7/9 subjects are currently still in the progression-free survival phase. The overall ORR assessed by RANO 2.0 was 33% (3/9) and DCR was 100% (9/9). All subjects (9/9, 100%) experienced the relieve of neurological functions, as measured by Japanese Orthopedic Association (JOA) Scores and McCormick Scores. Grade 3 drug-related treatment-emergent adverse events (TEAEs) occurred 2 times; and no grade 4 TEAEs occurred. **Conclusions:** Butaselen combined with standard radiotherapy was well tolerated, and exhibited meaningful prolongation of survival period, durable objective responses and neurological function improvements in primary H3K27M-mutant sDMG patients. Clinical trial information: ChiCTR2600116732. Research Sponsor: None.

Azeliragon, a RAGE inhibitor, plus temozolomide and radiotherapy in patients with newly diagnosed glioblastoma: Final results from a dose-finding phase in the CAN-201 NDG trial.

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Background: Radiotherapy (RT) plus temozolomide (TMZ) is the standard of care for patients (pts) with newly diagnosed glioblastoma (GBM). However, most eventually progress. The RAGE receptor and its ligands may contribute to RT resistance in GBM by sustaining chronic pro-tumorigenic inflammation, enhancing DNA damage repair pathways, and promoting survival signaling in hypoxic and stressed tumor cells. Azeliragon, an extensively studied RAGE inhibitor in Alzheimer's disease, may enhance overcome RT-TMZ resistance in newly diagnosed GBM. **Methods:** The CAN-201 NDG is an open-label, single-arm, phase Ib/II trial in Spain recruiting pts with newly diagnosed IDH-wildtype GBM. Pts received azeliragon in combination with standard RT-TMZ, followed by maintenance therapy with azeliragon. The trial consists of an initial dose-finding phase with a rolling six design and a subsequent expansion phase (up to 14 additional pts) at the recommended phase 2 dose (RP2D). The dose levels were 5 (L1), 10 (L2), 20 (L3), 30 (L4), and 50 (L5) mg/day. The primary objective was to determine the RP2D, defined as the dose for which <33% of pts experience dose-limiting toxicity (DLT) within 28 days of the initiation of dosing. Main secondary endpoints include progression-free survival (PFS), overall survival (OS), and changes in corticosteroid requirements. Pharmacokinetic and translational research is ongoing. **Results:** From Oct 2023 to May 2025, 33 pts were included across L1-L5 levels (6-8 pts per level). Median age was 56 years (range: 36-69). Most pts were male (66.7%), with ECOG 0-1 (93.9%), MGMT unmethylated (54.5%) and complete resection (45.5%). No DLTs occurred, and L5 (50 mg/day) was declared RP2D. One grade 3 maculopapular rash at L5 was the only serious adverse event related to azeliragon. Most common grade 3-4 toxicities were thrombocytopenia (21.2%) and lymphopenia (9.1%), all RT or TMZ-related. Most common possibly azeliragon-related AEs were asthenia (24.2%), nausea (21.2%), anorexia (9.1%), diarrhoea and dysgeusia (6.1% each), all grade 1-2. Median azeliragon treatment duration was 7.4 m (range: 2.7-21.1). Treatment ended due to disease progression (82.8%), toxicity (3.4%), and exitus (3.4%). Three pts at L5 remain on treatment. With median follow-up of 11 m (95% CI: 8.2-16.4), median PFS was 7.9 m (95% CI: 6.2-12.2) overall, 15.6 m (95% CI: 6.1-NR) and 6.7 m (95% CI: 5.0-10.9) for methylated and unmethylated MGMT, respectively. Median OS was not reached, 12m OS rate was 61.5% (95% CI: 4.4-85.3), with rates of 74.2% (95% CI: 52.4-100) and 51.1% (95% CI: 29.3-88.8) for methylated and unmethylated MGMT, respectively. **Conclusions:** Azeliragon at 50 mg/day in combination with standard RT / TMZ is safe, with no DLTs reported. More mature OS data will be presented. Further follow-up with a larger number of pts is required to assess preliminary efficacy. Clinical trial information: NCT05635734. Research Sponsor: CANTEX Pharmaceuticals, Inc.

Change in relative cerebral blood volume as a biomarker for early response to bevacizumab in patients with recurrent glioblastoma: ECOG-ACRIN EAF151.

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Background: Bevacizumab therapy (Bev) for recurrent glioblastoma (rGBM) has not demonstrated improved overall survival (OS) in randomized clinical trials. However, single-center and preliminary multi-center studies suggest that relative cerebral blood volume (rCBV) measured with dynamic susceptibility contrast MRI (DSC-MRI) at baseline or shortly after treatment initiation may predict response to Bev. The primary aim of ECOG-ACRIN EAF151 was to evaluate whether early binary change in rCBV, assessed 2–3 weeks after initiation of Bev-containing therapy, identifies patients with an OS benefit of ≥ 4 mos. Pre-specified secondary aims assessed baseline rCBV; post-hoc exploratory analyses examined early post-Rx rCBV. **Methods:** A prospective, phase II multi-center trial without randomization enrolled subjects with rGBM receiving their first Bev-containing therapy. Progression was determined by local sites (RANO criteria; MRI within 28 days of registration, ≥ 42 days since end of chemoradiation). Baseline (S0) and follow-up (S1) DSC-MRI were performed before the first Bev infusion (within 3 days), and 12–25 days post-infusion but before the second infusion. Anatomic MRI and DSC-MRI (double-dose Gadavist injection, full-dose preload) complied with recommended protocols. Mean normalized (nRCBV) and standardized (sRCBV) rCBV were extracted from contrast-enhancing tumor ROIs. A 2-sided logrank test ($\alpha=0.1$) was used to test the primary aim (change in mean nRCBV from S0 to S1, ≥ 0 vs. <0). Cox regression with restricted cubic splines was used to assess the association between continuous rCBV markers and OS. **Results:** 146 subjects were accrued from 33 sites. 134 completed S0 and 118 completed both S0 and S1. After exclusion of uninterpretable scans, 107 were evaluable for change in rCBV, and 124 for baseline rCBV. There was no statistically significant difference in OS between subjects with binary increase ($n=40$; median OS 8.0 mos [90% CI 5.5–9.2]) vs. decrease ($n=67$; 7.9 mos [90% CI 6.3–10.3]) in mean nRCBV ($p=0.67$). Based on the spline fits, we observed a strong nonlinear association between OS and continuous nRCBV and sRCBV at both S0 and S1: low marker values are associated with lower risk, but beyond a threshold, higher values are not associated with greater risk. As an exploratory analysis, we estimated optimal cut points (nRCBV: S0=1.11, S1=1.16; sRCBV: S0=1.13, S1=0.99) and found that subjects whose S1 rCBV decreased below threshold had a median OS 2.7 mos (nRCBV, HR 0.61 [90% CI 0.41–0.88]) and 5.2 mos (sRCBV, HR 0.43 [90% CI 0.28–0.63]) longer than subjects whose rCBV either increased or did not decrease below threshold. **Conclusions:** EAF151 prospectively evaluated whether DSC-MRI markers predict OS in patients with rGBM treated with Bev. Although the change in these markers was not predictive, both baseline and early post-Rx markers were predictive of OS. Clinical trial information: NCT03115333. Research Sponsor: National Cancer Institute; U10CA180820, U10CA180794, U10CA180821, U10CA180868, UG1CA232760, UG1CA233198, UG1CA233270, UG1CA233196, UG1CA233253.

Recurrence patterns and site-level survival in the previous phase III study of IL13-PE38QQR: Implications for drug distribution variability.

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Background: Interleukin-13–Pseudomonas Exotoxin A (IL13-PE38QQR) is a targeted cytotoxic fusion protein directed against the IL13 α 2 receptor expressed on glioblastoma stem cells and absent in normal brain tissue. The drug is administered by convection-enhanced delivery (CED) for recurrent glioblastoma (GBM). Early-phase studies demonstrated durable tumor control and long-term survival; however, a pivotal Phase III trial failed to meet its primary endpoint. We hypothesized that variability in clinical outcomes was driven primarily by limitations in drug delivery rather than tumor biology. **Methods:** We conducted a post hoc analysis of clinical, imaging, and survival data from the randomized Phase III PRECISE trial of IL13-PE38QQR versus Gliadel wafers. Treatment-site experience was defined as ≥ 3 efficacy-evaluable IL13-PE38QQR patients. A subset of patients underwent radiolabeled drug infusion to assess intraparenchymal distribution. Recurrence patterns were evaluated using serial MRI. Survival outcomes were compared by treatment arm and site experience. **Results:** Marked heterogeneity in drug distribution was observed in patients receiving radiolabeled IL13-PE38QQR, ranging from broad target coverage to minimal or absent delivery. In the IL13-PE38QQR arm, treatment at experienced centers correlated with significantly improved overall survival (median OS 48.4 vs 32.1 weeks; $p=0.038$), whereas site experience had no significant impact in the control arm. A 50% increase in 1-year survivorship was observed in the treatment arm compared with control. Long-term survivors most commonly exhibited distant or multifocal recurrence with relative preservation of the treated region, suggesting durable local tumor control where therapeutic exposure was achieved. **Conclusions:** Clinical outcomes following IL13-PE38QQR therapy were strongly associated with delivery efficiency and treatment-team experience. Radiolabeled distribution studies, experience-dependent survival effects, and recurrence patterns in long-term survivors indicate that outcome variability was driven primarily by technical limitations in drug delivery rather than tumor biology. This study represented the first large-scale evaluation of CED in the absence of purpose-built delivery technology, relying on complex, nonstandardized surgical workflows. These findings highlight the importance of standardized procedures, specialized training, and purpose-built delivery platforms to enable reproducible therapeutic exposure and optimize the clinical potential of IL13-PE38QQR. Clinical trial information: NCT00076986. Research Sponsor: None.

Scaling deep learning for neuro-oncology: Knowledge-distilled EfficientNetB0 powered MRI classification of brain tumors with international expert validation.

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Background: Accurate classification of brain tumors on magnetic resonance imaging (MRI) is critical for timely diagnosis, treatment planning, and referral in neuro-oncology. However, radiologic interpretation is challenged by tumor heterogeneity, overlapping imaging features, and growing imaging volumes, particularly in settings with limited subspecialty expertise. Although deep learning models have demonstrated high diagnostic accuracy, their computational complexity often limits real-world adoption. Scalable, resource-efficient AI systems capable of maintaining diagnostic performance are needed to enable global clinical translation.

Methods: We retrospectively assembled a multicontinental dataset of 5,000 brain MRI studies from six continents, including pituitary tumors (n=1,200), meningiomas (n=1,300), gliomas (n=1,400), and non-tumor controls (n=1,100). Ground-truth diagnoses were established through independent review by at least two expert neuroradiologists. A high-capacity EfficientNetB4 model served as the reference architecture. A lightweight EfficientNetB0 model was trained using structured knowledge distillation with soft probabilistic supervision to preserve diagnostic fidelity while reducing computational cost. Model performance was evaluated on internal test data and independent external datasets using accuracy, class-specific sensitivity and specificity, F1-score, and area under the receiver operating characteristic curve (AUROC).

Results: The distilled EfficientNetB0 model achieved an overall test accuracy of 94.8%, with balanced sensitivity across tumor classes (pituitary 93.1%, meningioma 95.2%, glioma 94.1%, non-tumor 96.4%). The overall F1-score was 0.946, and AUROC exceeded 0.92 on external validation datasets. Performance remained consistent across geographic regions and heterogeneous MRI acquisition protocols, with accuracy ranging from 93% to 96%. Mean inference time was 0.18 seconds per study on standard hardware, enabling real-time clinical integration. Clinician evaluators reported improved diagnostic confidence and utility for triage and workflow support. **Conclusions:** Knowledge-distilled EfficientNet models enable accurate, rapid, and computationally efficient classification of brain tumors on MRI without sacrificing clinically relevant performance. This scalable framework directly addresses key barriers to AI deployment in neuro-oncology and supports global implementation across resource-diverse settings. Prospective studies are planned to evaluate impact on diagnostic turnaround time, subspecialty access, and treatment decision-making. Research Sponsor: None.

Enabling hybrid AI–radiologist endpoints in clinical trials imaging workflows.

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Background: Imaging endpoints in oncology clinical trials commonly rely on a 2 + 1 radiologist reading paradigm, in which two independent readers perform primary assessments and a third adjudicates disagreements. This model underpins response evaluation frameworks such as RECIST and RANO, but is resource-intensive and contributes to trial cost, operational complexity, and inter-reader variability. Advances in transformer-based deep learning for 3D medical imaging enable hybrid AI–radiologist workflows that may preserve adjudicated oversight while reducing primary human reads. We evaluated the feasibility of replacing one primary radiologist reader with AI in a hybrid 2+1 imaging workflow, using glioma segmentation as a representative use case and with consideration for near-term integration into clinical trial imaging platforms such as Voiant Hub. **Methods:** A 3D SwinUNETR open-source deep learning model implemented using the MONAI framework pre-trained to segment glioma subregions from multimodal MRI, including enhancing tumor and non-enhancing/edema components. Model performance was assessed using Dice similarity coefficients across a multi-case dataset, complemented by qualitative review of representative cases spanning high-agreement and high-discordance scenarios. Two reading paradigms were evaluated conceptually: (1) traditional radiologist–radiologist + adjudicator, and (2) AI–radiologist + adjudicator. AI–radiologist segmentation divergence was used as a proxy for adjudication likelihood and workflow impact. **Results:** AI segmentation demonstrated substantial concordance with reference contours in well-defined enhancing tumor regions, with performance variability reflecting known biological heterogeneity. Dice scores for enhancing tumor reached values as high as 0.80, with a broad distribution across cases. Qualitative review showed that AI–radiologist disagreements were most commonly associated with small-volume lesions, infiltrative margins, or low-contrast regions: patterns similar to known human inter-reader variability. The presence of an adjudicator preserved clinical oversight for discrepant cases while eliminating the need for a second full human primary read. **Conclusions:** A hybrid AI–radiologist 2+1 imaging workflow is feasible for glioma volumetric assessment and has broader implications for RECIST- and RANO-based endpoints in oncology clinical trials. Substituting AI for one primary radiologist reader preserves adjudicated decision-making while reducing manual read burden. The availability of configurable, regulator-aligned imaging platforms such as Voiant Hub positions this hybrid approach as a near-term, easily adoptable evolution of current reading paradigms. Prospective evaluation is warranted to quantify operational impact, adjudication rates, and endpoint consistency across solid tumor and neuro-oncology trials. Research Sponsor: None.

Impact of genomic subtype on intracranial outcomes in treatment-naïve *EGFR*-mutant NSCLC with osimertinib (IGNITE).

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Background: Osimertinib is the standard first-line therapy for *EGFR*-mutant NSCLC with brain metastasis (BM); however, alteration-specific patterns of CNS failure and mortality in treatment-naïve patients remain poorly defined. **Methods:** We assembled an international multi-institutional cohort of TKI and radiation-naïve *EGFR*-mutant NSCLC patients with BM treated with first-line osimertinib, with or without upfront stereotactic radiosurgery (SRS) (within 2 months of BM diagnosis). The primary endpoint was time to CNS progression. Time-to-event outcomes were analyzed using the Kaplan-Meier method. Multivariable hazard ratios (MHR) were estimated using Cox proportional hazards models. Fine and Gray hazard models were used for endpoints with competing risks. **Results:** From 2016–2024, 470 patients from 11 institutions were identified with the following alterations: exon 19 deletion (57%), L858R mutations (33%), and atypical/uncommon mutations (9.6%). Median follow-up was 25.6 months (IQR, 14.7–41.3 months). At 24 months, the cumulative incidence of CNS progression was 30% for exon 19 deletions, 47% for L858R mutations (MHR 1.68, $p < 0.001$), and 76% for atypical mutations (MHR 4.33, $p < 0.001$). Atypical alterations experienced markedly shorter time to local failure (MHR 4.88, $p < 0.001$). Compared to exon 19 deletions, L858R (MHR 1.73, $p = 0.001$) and atypical alterations (MHR 2.86, $p < 0.001$) were associated with shorter time to distant CNS progression. L858R was also associated with higher risk of leptomeningeal disease (MHR 2.49, $p = 0.001$). At 24 months, cumulative incidence of neurological death was 4.6% for exon 19 deletions, 7.8% for L858R, and 9.1% for atypical alterations ($p = 0.023$). Upfront SRS was associated with improved CNS outcomes, with greater benefit for patients in L858R and atypical alterations. **Conclusions:** In the largest multi-institutional study of treatment-naïve *EGFR*-mutant NSCLC with BM treated with first-line osimertinib, *EGFR* alteration subtype was an independent determinant of CNS progression, defined patterns of CNS failure, and identified patients most likely to benefit from treatment intensification with SRS. Research Sponsor: National Cancer Institute; P30-CA008748.

Burden of mortality due to brain metastases secondary to lung cancer in the United States: A population-based study.

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Background: Brain metastasis is a common and severe complication in lung cancer, contributing significantly to morbidity and mortality. Despite therapeutic advances, the burden remains substantial. This study examines mortality trends, disparities, and geographic variation using CDC WONDER data in the United States. **Methods:** We accessed the CDC WONDER Multiple Cause of Death database (1999–2023) to identify individuals who died of brain metastasis (ICD-10: C79.3) among lung cancer patients (ICD-10: C34.0–C34.9). Mortality disparities were examined by year, sex, race/ethnicity, and geography. Age-adjusted mortality rate (AAMR) per 100,000 was calculated. Joinpoint regression was used to estimate the average annual percentage change (AAPC) and annual percentage change (APC), with 95% confidence intervals (CIs). **Results:** The total of 207,151 deaths related to brain metastasis among lung cancer patients. Overall, the AAMR slightly decreased from 4.95 (95% CI: 4.85–5.05) in 1999 to 3.62 (95% CI: 3.55–3.69) in 2023 (AAPC: -1.40; 95% CI: -1.82 to -0.99, $p < 0.000001$). The trend initially declined, followed by an upward trajectory between 2013 and 2017 (APC: 3.03; 95% CI: 1.00 to 5.10), after which it remained relatively stable till the end of the study period (APC: 0.33; 95% CI: -0.29 to 0.95). The decrease in mortality was slightly more pronounced in men than in women (AAPC: -2.03 vs -0.74). The highest incidence rates were noted among non-Hispanic (NH) Whites, followed by NH Blacks or African Americans and NH Asians and Pacific Islanders. Geographic disparities were apparent, with the South experiencing the greatest impact, while the Northeast was the least affected. Rural regions consistently showed higher AAMR compared to urban areas, while urban locations experienced a steeper decline between the two (AAPC: -1.95 vs -0.92). **Conclusions:** Mortality from brain metastasis in lung cancer patients has slightly declined over the past two decades, with greater reductions observed in men. However, persistent disparities across race, geography, and rural-urban populations underscore the urgent need for targeted interventions and equitable healthcare strategies to achieve favorable outcomes. Research Sponsor: None.

Deaths and AAMR per 1,000,000 for trends related to lung cancer with brain metastasis, 1999 to 2023.

Variable	Deaths	AAMR (95%CI) 1999	AAMR (95% CI) 2023
Overall	207,151	4.95 (4.85 to 5.05)	3.65 (3.55 to 3.69)
Male	108,179	6.25 (6.07 to 6.42)	3.85 (3.74 to 3.96)
Female	98,972	3.98 (3.85 to 4.10)	3.41 (3.32 to 3.50)
NH White	176,368	5.17 (5.06 to 5.29)	4.05 (3.96 to 4.14)
NH Black	22,609	6.10 (5.71 to 6.48)	3.63 (3.41 to 3.85)
NH Asians	5,762	2.29 (1.84 to 2.73)	2.68 (2.42 to 2.94)
South	88,589	5.40 (5.22 to 5.59)	3.94 (3.82 to 4.06)
Northeast	30,890	4.60 (4.38 to 4.82)	2.64 (2.49 to 2.78)
Metro	120,044	1.51 (1.44 to 1.57)	(2020) 5.33 (5.23 to 5.42)
Non metro	27,540	1.39 (1.27 to 1.52)	6.17 (5.94 to 6.41)

Risk of developing brain/central nervous system (CNS) metastases across multiple *ERBB2*-altered cancer types: Genotype as shaper of phenotype.

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Background: *ERBB2* (HER2) alterations are associated with increased risk of brain metastases in breast cancer and non-small cell lung cancer (NSCLC). However, the relationship between *ERBB2* alterations and brain metastasis across other tumor types remains unclear. We hypothesized that *ERBB2*-altered tumors demonstrate increased propensity for brain metastases across multiple cancer types. **Methods:** Using the US-based deidentified Flatiron Health-Foundation Medicine Clinico-Genomic Database (FH-FMI CGDB), we analyzed patients with advanced solid tumors who received ≥ 1 line of therapy. *ERBB2* alterations included pathogenic/likely pathogenic variants and amplifications. Brain/CNS metastases were identified via ICD-9/10 codes and validated against manual abstraction in NSCLC patients. Focusing on patients without brain/CNS metastases at diagnosis, we performed Cox proportional hazards analyses to evaluate time from initial diagnosis to first brain/CNS metastasis, modeling death as a competing risk. Multivariable models were adjusted for tumor types. **Results:** The analysis included 47,653 patients across 16 tumor types. Excluding breast/NSCLC, there were 29,272 patients: 2,149 *ERBB2*-altered (7.3%) and 27,123 *ERBB2*-wild type. 653 patients (30% of *ERBB2*-altered patients) had mutations and 1644 patients (77%) had amplifications (some had both). In a multivariable analysis adjusting for tumor type and excluding breast/NSCLC, *ERBB2* alterations independently predicted accelerated brain/CNS metastasis development (HR 1.55, 95% CI 1.29–1.86, $p < 0.001$). In separate disease-specific Cox models, the strongest associations were observed in gastric (HR 2.33, 95% CI 1.68–3.22, $p < 0.001$) and ovarian cancers (HR 2.52, 95% CI 1.45–4.38, $p < 0.001$) as well as breast (HR 1.70, 95% CI 1.48–1.96, $p < 0.001$) and NSCLC (HR 1.33, 95% CI 1.11–1.60, $p = 0.002$). **Conclusions:** *ERBB2* alterations predict a significantly increased risk of accelerated development of brain/CNS metastases independent of tumor types, with the strongest effects observed in gastric and ovarian cancers in addition to breast and lung cancers. Research Sponsor: None.

AI-assisted prediction of radiation failure patterns and survival after stereotactic radiosurgery for brain metastases: A multicenter study.

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Background: Brain metastases occur in approximately 20%–40% of patients with cancer and are associated with substantial morbidity and mortality. Stereotactic radiosurgery (SRS) is an effective and widely used treatment; however, a significant proportion of patients experience local, distant, or leptomeningeal failure after treatment. Early prediction of radiation failure patterns is critical for guiding individualized surveillance and treatment strategies. Current clinical tools remain inadequate for accurately predicting radiation failure in patients with brain metastases. **Methods:** In this multicenter retrospective study, we included 1,079 patients with brain metastases from three medical centers. We developed a novel deep learning model, the Global-to-Local Multiple-Instance Learning Mixture-of-Experts (GL-MIL MoE) framework. The model integrates a mask-guided multiscale encoder to process global MRI volumes and a multiple-instance learning (MIL) module to extract features from high-resolution local tumor patches. The primary endpoint was radiation failure pattern, defined as local failure, distant failure, or leptomeningeal failure. The secondary endpoint was overall survival (OS). Model performance was evaluated using the area under the receiver operating characteristic curve (AUC), concordance index (C-index), and decision curve analysis (DCA). Model interpretability was assessed using SHAP (Shapley Additive Explanations) and Grad-CAM analyses. **Results:** The proposed AI model demonstrated strong and consistent performance, achieving AUCs ranging from 0.78 to 0.83 across validation cohorts. C-indices for OS prediction remained robust and significantly outperformed established baseline models ($p < 0.05$). Multivariable logistic and Cox regression analyses confirmed the model-derived risk score as an independent predictor of both radiation failure patterns and OS ($p < 0.05$). The model effectively stratified patients into high- and low-risk groups across all cohorts. Decision curve analysis demonstrated meaningful and consistent clinical utility. **Conclusions:** This AI-based deep learning model enables accurate prediction of radiation failure patterns and survival in patients with brain metastases treated with SRS. Prospective studies are warranted to evaluate its clinical utility in guiding personalized treatment and surveillance strategies in combination with standard clinicopathologic factors. Research Sponsor: None.

Preclinical activity of homoharringtonine against melanoma leptomeningeal disease using patient-derived tumor cells.

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Background: Leptomeningeal disease arising from melanoma (M-LMD) is a rare and highly aggressive form of metastasis associated with limited therapeutic options and poor clinical outcomes. Progress in treatment development has been hindered by the lack of clinically relevant models, particularly patient-derived circulating tumor cells obtained from cerebrospinal fluid (PD-CSF-CTCs). To overcome this limitation, we established protocols for CSF and tissue collection from patients with M-LMD, enabling successful *ex vivo* propagation of PD-CSF-CTCs and the generation of patient-derived xenograft models. These platforms facilitated integrated proteomic and transcriptomic analyses to identify M-LMD-specific pathways, thereby supporting the discovery of targeted therapeutic strategies. **Methods:** PD-CSF-CTCs were propagated from samples obtained from the CSF of patients with M-LMD. A library of 1,436 FDA-approved small molecules was screened using a high-throughput 384-well assay to identify agents that suppressed tumor cell proliferation. Lead compounds were subsequently assessed *in vivo* through intrathecal administration in xenograft models. **Results:** Twenty compounds (~1.4%) demonstrated complete cytotoxicity in both PD-CSF-CTCs and murine melanoma cell lines. The most potent agents included ponatinib (EC_{50} : $1.85-4.06 \times 10^{-6}$), sorafenib ($9.57-9.77 \times 10^{-6}$), ceritinib ($1.84-2.05 \times 10^{-6}$), and homoharringtonine (HHT; $3.63-4.11 \times 10^{-6}$). HHT, a plant-derived semisynthetic cephalotaxine ester, was prioritized for *in vivo* evaluation based on its robust cytotoxic activity and capacity to penetrate both the blood-brain and blood-CSF barriers. In a randomized murine M-LMD model, daily intrathecal administration of HHT (24.0 μ g) was well tolerated, significantly prolonged survival ($P < 0.001$, Mantel-Cox test), and achieved complete responses in 27% of treated mice, while preserving body weight and motor function. **Conclusions:** This study introduces a robust preclinical platform for identifying effective treatments for M-LMD. Our findings highlight the promise of repurposing FDA-approved HHT as a therapeutic option. Future work will focus on refining HHT's activity against M-LMD and elucidating HHT's molecular mechanisms. Research Sponsor: None.

The impact of various radiation therapy options on plasminogen activation markers in the blood of patients with metastatic brain lesions.

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Background: Metastatic brain disease (MBD) is found in almost a third of patients with malignant neoplasms and is characterized by a high mortality rate. The role of the fibrinolytic system has been demonstrated in neoplasms of various locations, while tissue plasminogen activator (t-PA) is studied less frequently than urokinase activator. The aim of this study was to investigate the level and activity of t-PA in the blood of patients with MBD receiving different radiotherapeutic treatments. **Methods:** Plasma from 38 patients of both sexes, aged 59.9 ± 8.9 years, with brain metastases confirmed by magnetic resonance imaging (MRI), was analyzed using enzyme-linked immunosorbent assay (ELISA) to determine t-PA activity and levels, calculate the ratio between them, and determine parameters of type 1 plasminogen activator inhibitor (PAI-1) and the receptor for both plasminogen activators (uPAR). The results were compared with data from 18 individuals without cancer (a donor group). Three groups were formed based on the treatment regimens: Control — stereotactic radiotherapy at the site of the resected metastasis with a single fraction dose (SFD) of 6 Gy up to a total dose of 30 Gy; Main Group No. 1 — after a preoperative radiosurgery session with an SFD of 10–15 Gy, the metastatic lesion was removed 24 hours later; Main Group No. 2 — staged radiosurgery (SRS) was performed in 3 sessions with an SFD of 10 Gy at 14-day intervals (total dose of 30 Gy). **Results:** Before treatment, a 2.1-fold increase in t-PA activity was observed in the blood of patients with MBD. This, together with a 3.6-fold reduction in t-PA content, led to a 10-fold increase in their ratio ($p \leq 0.0002$). Meanwhile, urokinase activator activity did not change. In the control group, t-PA activity remained elevated three days after surgery and did not differ from donor levels one month later, while t-PA levels remained reduced. In both main groups, elevated t-PA activity relative to donors was observed throughout the entire observation period, and after one month, it was 2.6 times higher than in the control group ($p \leq 0.001$). Only patients receiving SRS were characterized by an increase in the initially reduced t-PA content, with a change toward normalization of the t-PA activity-to-content ratio. This was accompanied by an increase in the activity of inhibitor PAI-1 and receptor uPAR to donor levels. **Conclusions:** The revealed dynamics of t-PA and PAI-1 parameters in SRS compared with other types of radiation therapy may be one of the factors contributing to the greater positive clinical efficacy of this developed method of staged radiotherapy in the treatment of metastatic brain tumors. Research Sponsor: None.

Cerebrospinal fluid biomarker profiling in patients with non–small cell lung cancer and leptomeningeal disease.

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Background: Cerebrospinal fluid (CSF) cytology remains the standard for diagnosing leptomeningeal disease (LMD) and monitoring treatment response, but its clinical utility is limited by low sensitivity and nonquantitative results. The role of novel CSF biomarkers, such as circulating tumor cells (CTCs), in improving disease assessment in non–small cell lung cancer (NSCLC) with LMD is not fully defined. **Methods:** We performed retrospective clinical and genomic analysis of patients with NSCLC and LMD who underwent CSF CTC testing using the CellSearch platform at Memorial Sloan Kettering between 1/1/2015 and 11/5/2025. Time-to-event analyses were calculated from initial positive CSF CTC measurement (≥ 3 cells/3mL) or from completion of proton craniospinal irradiation (pCSI). Optimal CTC cutoffs were determined using recursive partitioning analysis (RPA). CSF cytologic clearance was defined as an initial positive cytology followed by two consecutive negative results at least 4 weeks apart. Next-generation sequencing was performed using MSK-IMPACT. **Results:** Among 148 patients with NSCLC and LMD, 72% (n=105) were female, 53% (n=78) were never-smokers, and 92% (n=136) harbored an oncogenic driver alteration, most commonly epithelial growth factor receptor (*EGFR*) mutations (60%, n=89). Fourteen percent (n=20) were diagnosed with LMD at time of metastatic disease, whereas 54% (n=80) had received 2 or more prior lines of therapy. Sixty-two percent (n=92) received radiation therapy for LMD, including 43% (n=64) undergoing pCSI and 18% (n=26) undergoing photon radiation (involved field radiation therapy [IFRT] to brain/spine, n=10; whole brain radiation therapy [WBRT] alone, n=10; WBRT + IFRT to spine, n=4; photon CSI, n=2). With a median follow-up of 21.6 months (95% CI 16.2–37.9), patients with a lower baseline CSF CTC count (≤ 90 CTCs/3mL, n=66; cutoff identified through RPA) had longer median overall survival (mOS; 10.2 vs 6.6 months; HR 0.53, 95% CI 0.35–0.79; $p=0.002$) compared with those with higher counts (>90 CTCs/3mL, n=82). Among patients who underwent pCSI with serial CSF testing (n=34), a $\geq 30\%$ reduction in CTCs was associated with a longer mOS (13.1 vs 6.2 months; HR 0.15, 95% CI 0.05–0.47; $p=0.0001$) compared with those with $<30\%$ reduction; only 12% (n=4) achieved CSF cytologic clearance. In *EGFR*-mutant NSCLC, genomic analysis of CSF samples with higher baseline CTC count (>90 CTCs/3mL, n=24) demonstrated a higher frequency of *TP53* ($p=1.559e-3$) and *MTAP* ($p=8.31e-3$) alterations, and a lower frequency of *MDM2* ($p=0.05$) alterations, compared to patients with lower baseline CTC counts (≤ 90 CTCs/3mL, n=23). **Conclusions:** Lower baseline CSF CTC counts and reductions following pCSI are associated with improved survival in patients with NSCLC and LMD. CSF CTC assessment provides a quantitative measure of LMD burden and may complement conventional CSF cytology. Research Sponsor: None.

Preclinical efficacy and brain uptake of an insulin-mediated nanoparticle co-delivering trastuzumab and pertuzumab (AxS007) in HER2+ breast cancer brain metastasis models.

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Background: Anti-HER2 antibodies are standard therapies for metastatic HER2+ breast cancer but demonstrate limited intracranial activity due to restricted penetration across the blood-brain barrier (BBB). AxS007 is an insulin-mediated nanoparticle conjugated to trastuzumab and pertuzumab designed to enhance BBB transport and increase brain exposure. **Methods:** Brain uptake and distribution were assessed in C57BL mice using biodistribution analysis (5 min–90 days, n=25) and two-photon microscopy, comparing AxS007, a non-insulin-conjugated nanoparticle control, and free trastuzumab. Brain uptake was also evaluated in non-human primates (NHPs). Based on confirmed BBB penetration and brain exposure, AxS007 antitumor activity was evaluated in vitro in HER2+ cell lines (BT474, SKBR3, N87) and in vivo in BT474 subcutaneous (SC; n=20) and intracranial xenografts. Tumor growth inhibition (TGI) was assessed by MRI, and survival was compared between vehicle, AxS007 (IV, 10 mg/kg), and free trastuzumab + pertuzumab (IV, 10 mg/kg each). Safety was further investigated through single ascending dose (SAD) and multiple ascending dose (MAD) toxicological studies. **Results:** In mice, AxS007 demonstrated measurable brain uptake within 30 min and widespread parenchymal distribution at 24 h, with markedly higher brain exposure than free trastuzumab; in contrast, the non-insulin control and free antibodies showed minimal BBB crossing. In NHPs, AxS007 increased brain antibody exposure ~50-fold versus free antibodies at 48 h. In vitro, AxS007 showed antitumor activity comparable to or greater than free antibodies (SKBR3: 90% vs 50%; BT474: 50% vs 64%). In vivo, AxS007 achieved near-complete tumor elimination in SC tumors and demonstrated 82% TGI versus vehicle ($p<0.01$) and 60% TGI versus free trastuzumab + pertuzumab ($p<0.05$) in intracranial tumors, as assessed at day 60 post-inoculation. In an overall survival study, AxS007 extended survival approximately 3-fold compared with free trastuzumab + pertuzumab. AxS007 exhibited a good safety profile with no drug related side effects. **Conclusions:** AxS007 showed enhanced BBB penetration and increased brain antibody exposure, with improved preclinical efficacy versus free antibodies in HER2+ breast cancer brain metastasis models. These findings support further translational advancement of AxS007 toward first-in-human clinical testing. Research Sponsor: Nanocarry Therapeutics Ltd.

Real-world outcomes of systemic therapy sequencing after earlier-generation EGFR TKI failure in NSCLC with brain metastases.

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Background: Patients with EGFR-mutated non-small cell lung cancer (NSCLC) frequently develop BM, and CNS progression is a common mode of failure on earlier-generation EGFR tyrosine kinase inhibitors (TKIs). After TKI failure in the setting of BM, optimal next-line systemic therapy remains uncertain, particularly regarding the comparative effectiveness of targeted escalation, immunotherapy (IO)-based regimens, and chemotherapy. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network. We identified EGFR-mutated NSCLC patients treated with first- or second-generation EGFR TKIs who subsequently developed metachronous BM and initiated next-line systemic therapy between 2015 and 2025. Patients with leptomeningeal disease prior to earlier-generation TKI exposure were excluded. Treatment strategies were categorized as targeted escalation with osimertinib, IO-based therapy (immune checkpoint inhibitor with or without chemotherapy), or chemotherapy alone. The index date was defined as initiation of next-line systemic therapy. Propensity score matching was performed for pairwise comparisons. The primary endpoint was overall survival (OS) at 180 days. Restricted mean survival time (RMST) through 181 days was evaluated as a sensitivity analysis. Baseline covariate balance after matching was assessed using standardized mean differences, with values <0.10 indicating adequate balance. **Results:** After propensity score matching with adequate baseline balance, osimertinib was associated with significantly lower 180-day mortality compared with chemotherapy (24.5% vs 33.2%; hazard ratio [HR] 0.69, 95% CI 0.47–1.00). Comparisons between osimertinib and IO-based therapy showed numerically lower 180-day mortality with osimertinib (26.0% vs 32.6%; HR 0.79, 95% CI 0.54–1.15), but this difference did not reach statistical significance. Similarly, IO-based therapy was not associated with a statistically significant survival advantage compared with chemotherapy alone (31.7% vs 37.5%; HR 0.78, 95% CI 0.58–1.06). RMST analyses for death over 181 days were directionally consistent with hazard ratio-based results, with modest, non-significant differences in mean survival time. **Conclusions:** In EGFR-mutated NSCLC patients with metachronous brain metastases after earlier-generation TKI failure, targeted escalation with osimertinib was associated with significantly lower 180-day mortality compared with chemotherapy. IO-based approaches demonstrated intermediate, directionally favorable but non-significant outcomes relative to both osimertinib and chemotherapy. These real-world findings support guideline recommendations prioritizing next-generation TKIs and help inform systemic treatment sequencing in a CNS-enriched population where prospective data remain limited. Research Sponsor: None.

Low-density lipoprotein receptor–related protein 1 overexpression as an identifier of brain metastasis and survival for patients with lung cancer.

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Background: Brain metastasis (BM) is a major cause of mortality in lung cancer. Low-density lipoprotein receptor–related protein 1 (LRP1) has been implicated in tumor invasion and microenvironment regulation; however, its clinical relevance in lung cancer brain metastasis remains unclear. **Methods:** This retrospective, single-center study included 103 lung cancer patients (including NSCLC and SCLC) diagnosed between January 2013 and February 2025. LRP1 protein expression was evaluated by immunohistochemistry in primary lung tumors and lesions of lung cancer with brain metastasis (unpaired samples). Mean optical density was quantified, and the optimal cutoff for high versus low expression was determined using receiver operating characteristic analysis. Overall survival (OS) and distant metastasis–free survival (DMFS) were assessed using Kaplan–Meier analysis and Cox proportional hazards models, adjusting for pathological type, age, sex, T stage, and N stage. Gene set variation analysis (GSVA), immune cell infiltration analysis (CIBERSORT), and immunotherapy response prediction using TIDE were performed to explore biological characteristics associated with LRP1 expression. **Results:** LRP1 expression was significantly higher in lung cancer tissues from patients with BM compared with those without BM ($P < 0.0001$). Among patients with BM, high LRP1 expression was associated with poorer OS ($P = 0.0352$) and shorter DMFS ($P = 0.0183$). In multivariable analysis, high LRP1 expression remained independently associated with inferior OS (HR 3.064, 95% CI 1.039–9.034; $P = 0.042$). GSVA suggested that LRP1-high tumors may be characterized by enrichment of TGF- β , NOTCH, and HEDGEHOG signaling pathways. Immune deconvolution analysis revealed higher infiltration of resting memory CD4⁺ T cells and M0 macrophages in the LRP1-high group. LRP1-low expression was associated with a more favorable predicted response to immunotherapy, as indicated by lower TIDE scores. **Conclusions:** LRP1 overexpression is associated with brain metastasis, unfavorable survival, and distinct immune features in lung cancer, suggesting its potential value as a prognostic biomarker. Research Sponsor: None.

Neoantigen prediction and reactivity of cerebrospinal fluid–human-derived tumor reactive T cells (CSF-TRT cells) in leptomeningeal disease (LMD) from solid tumors.

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Background: Leptomeningeal disease (LMD) is a devastating complication of metastases and its incidence is increasing. Adoptive cell therapy (ACT) using tumor-infiltrating lymphocytes (TILs) showed complete responses in patients with metastatic melanoma and other solid tumors. To obtain CSF-TRT cells as a source of T cells for ACT, we aim 1) to identify the expansion method that allows higher expansion of tumor reactive TIL; 2) to enrich tumor neoantigen reactive TILs and determine their in-vivo and ex-vivo functional capabilities.

Methods: Cells were isolated from 64 CSF collections from melanoma (M-LMD), 9 CSF from breast cancer (B-LMD), and 9 CSF from lung adenocarcinoma (L-LMD) from patients with LMD. Cells were plated following established TIL culture protocols (high-dose IL-2): 1) OKT3, 2) anti-4-1BB-agonist, 3) IL-7+IL-15+IL-21, 4) anti-CD3/CD28-T-activator, 5) anti-CD3/CD28/CD137-T-activator, 6) anti-CD3/CD28-T-expander. After 4–6 weeks, reactivity was assessed with HLA-matched or autologous tumor cells. Additionally, Whole Exome Sequencing (WES) and RNA sequencing were performed in T cells expanded from CSF and pair-matched extracranial tumors from 12 patients with M-LMD for epitope prediction to identify neo-antigens that may be targets of immunoediting using computational algorithms. **Results:** CSF yielded an average of 1.204×10^5 viable cells for expansion. After culture in IL-2, 53.4% of samples showed increased cell yield with average 165.29-fold expansion. PreREP resulted in 37.6% CD8+ T cells. REP had a 96.8% success rate (mean 589.87-fold expansion). Post-REP flow cytometry revealed expansion of CD4+ T cells. Additional cultures produced similar yields with reduced T cell input requirement and demonstrated the potential to enrich for CD8+ T cells. Out of five samples tested for reactivity to HLA-matched melanoma cell lines, three produced varying levels of IFN- γ . T cells expanded from CSF samples from L-LMD and B-LMD had less successful results. L-LMD had a success expansion rate of 11.1% with IL-2 only, 83.3% with T-Activator, 50% with CD127 T Activator, and 50% with T-Expander. B-LMD had a success rate of 22.2% with IL-2 only, 0% with OKT3, 83.3% with T-Activator, 50% with CD137 T-Activator, and 85.7% with T-Expander. One of the CSF samples from L-LMD tested showed reactivity to autologous HLA-matched tumor cells, whereas none of the CSF T cells from B-LMD showed a successful reactivity. Preliminary studies demonstrated CSF TIL reactivity against tumor re-active neoantigens. Ongoing studies will confirm our results. **Conclusions:** Results demonstrate successful expansion of T cells *ex vivo* from CSF in M-LMD, raising the potential to use CSF-derived T-cells as therapeutic strategy for LMD. There was a variable success rate with expansion of T cells from CSF from B-LMD and L-LMD and supplementary studies are needed. Research Sponsor: None.

Intracranial pharmacokinetics and resistance mechanisms of tucatinib in patients with HER2+/mutant solid tumors and brain metastasis: Results from the WinHER2 study (NCT05892068).

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Background: Tucatinib, a potent HER2-selective tyrosine kinase inhibitor approved for the treatment of HER2-positive (+) metastatic breast cancer (MBC) and colorectal cancer (CRC), has demonstrated activity in stable and active brain metastasis (BrM). However, intracranial pharmacokinetics and specific mechanisms of resistance driving BrM progression remain unknown. **Methods:** This window-of-opportunity, prospective, non-randomized study evaluated tissue and serum levels of tucatinib ([Tt], [Ts]) in patients undergoing BrM resection for HER2+/mutant (mut) MBC, NSCLC, CRC or gastroesophageal cancer. HER2+ MBC patients were enrolled in 2 parallel cohorts: those with progressing BrM while on tucatinib (A) and tucatinib-naïve patients (B); cohort C was comprised of patients with GI malignancy, NSCLC and mutHER2 MBC. All patients received tucatinib 300 mg BID for 4 days preoperatively. [Tt/s] were measured by mass spectrometry in resected BrM and serum at screening and 3 intra-operative timepoints; CSF [T] was collected when available by optional lumbar puncture. BrM tissue was used for correlative studies including WGS, scRNA-seq, and electron microscopy. The primary endpoint compared BrM-to-serum tucatinib ratios between cohorts A and B with lower ratios hypothesized in cohort A. [T] was reported as median and interquartile range (IQR). **Results:** 9 female patients enrolled between 7/2023 and 12/2025: 3 in cohort A, 5 in cohort B, and 1 HER2+ CRC patient in cohort C. Median age was 48.5 years (43–65). One patient from cohort B was unevaluable due to lack of viable recurrent disease on pathologic examination. Total tucatinib levels in resected BrMs ranged from 2.22 to 192.87 ng/mg, (median=30.82; IQR=16.52–111.84) in cohort A and from 1.5 to 4.21 ng/mg (median=3.04; IQR=1.93–4.05) in cohort B. The median tucatinib serum concentration was 1158.3 ng/mL (range=229.2–3440; IQR=693.78–2299.17) and 365.52 ng/mL (range=167.23–731.03; IQR=176.47–596.37), in cohorts A and B, respectively. The BrM/serum ratio did not differ between cohorts A and B (median=9.7; range=9.0–166.5; IQR=9.43–102.77] vs 7.36 [range=3.77–22.28; IQR=5.26–12.30]). The single cohort C patient had tucatinib BrM level of 1.66 ng/mg and BrM/serum ratio of 7.41. CSF [T] was available in two cohort A patients: it was undetectable in one and 35.71 ng/mL in the other (BrM/CSF ratio: 54.01). **Conclusions:** Patients with progressing BrM while receiving tucatinib had BrM/serum tucatinib ratios similar to those of patients receiving tucatinib for the first time in the trial. These data indicate that intratumoral drug concentration alone is unlikely to account for intracranial acquired resistance. Correlative analyses investigating potential genomic and microenvironmental mechanisms of resistance are ongoing, and results will be presented at the meeting. Clinical trial information: NCT05892068. Research Sponsor: Pfizer.

Genomic correlates of leptomeningeal disease after brain metastasis resection.

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Background: Leptomeningeal disease (LMD) remains a frequent and devastating pattern of failure following surgical resection of brain metastases (BM), occurring in up to one-third of patients despite optimal local therapy. Although mechanical disruption of BM tissues may increase the risk of subsequent LMD, the underlying biologic determinants of postoperative LMD remain undefined. This study aims to identify genomic alterations in resected BM and their association with LMD development using the largest craniotomy cohort to date with paired next-generation sequencing and longitudinal CNS outcomes data. **Methods:** We retrospectively identified patients who underwent surgical resection and MSK-IMPACT next-generation sequencing of one or more BM. LMD was diagnosed using brain and spine MRI and CSF cytology and classified as either classical LMD (cLMD; diffuse coating of meningeal spaces and/or positive CSF cytology), nodular LMD (nLMD; discrete nodular deposits with negative CSF cytology), or both. Fine-Gray subdistribution hazard (sHR) estimated the cumulative incidence of LMD, treating death as a competing risk. **Results:** Among 1,006 patients, NSCLC (360, 36%), breast (181, 18%), and melanoma (128, 13%) predominated; most patients had single (530, 53%), supratentorial (796, 79%), and large (>2cm, 886, 88%) BM, and underwent postoperative cavity radiotherapy (890, 88%). Median follow-up and OS were 24.8 and 21.5 months, respectively. The cumulative incidence of LMD was 31% (cLMD 18%, nLMD 19%) at 2 years, with the highest rates seen in breast cancer patients (45% LMD; cLMD 28%, nLMD 23%). Median time to cLMD and nLMD were 7.7 and 6.4 months, respectively. Median OS after cLMD and nLMD diagnosis were 5.7 and 12 months, respectively. The most frequently altered genes in resected BM were TP53 (62%), CDKN2A (25%), TERT (23%), KRAS (20%), ERBB2 (12%), PIK3CA (12%), PTEN (12%), and RB1 (11%). In a pan-cancer analysis, alterations in CDH1 (sHR 3.0, $q=0.03$), EGFR (HR 2.5, $q<0.001$), GATA3 (sHR 2.2, $q=0.03$), or RB1 (sHR 1.7; $q=0.04$) were associated with an increased risk of cLMD; alterations in PTEN were associated with an increased risk of nLMD (sHR 1.8, $q=0.02$). Within breast and lung cohorts, alterations in RB1 or EGFR, respectively, were associated with an increased risk of cLMD. BM from patients who developed LMD exhibited greater genomic instability, with a higher fraction of the genome altered compared to those who did not (0.47 vs 0.40, $p<0.001$). **Conclusions:** LMD is a common and deadly form of progression following BM resection. Distinct genomic features, present in the resected BM specimen, may identify patients at increased risk of LMD. These findings support the development of a clinicogenomic model to select BM patients for intensified surveillance and postoperative care. Research Sponsor: U.S. National Institutes of Health; P30 CA008748.

Distinct genomic and microenvironmental profiles of brain metastases in renal cell carcinoma: Insights into hypoxia-driven adaptation and therapeutic vulnerabilities.

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Background: Brain metastases (BM) in renal cell carcinoma (RCC) are associated with poor prognosis and may exhibit unique genomic alterations influenced by the tumor microenvironment (TME), differing from primary tumors or extracranial metastases (ECM). This study aimed to characterize these differences to identify potential therapeutic targets. **Methods:** 3,913 RCC samples underwent NGS of DNA and RNA at Caris Life Sciences (Phoenix, AZ) and were linked to corresponding insurance claims data. Real-world overall survival (rwOS) was calculated from the date of sample collection to last contact using Cox PH model and log-rank testing. Genomic alterations were compared at an adjusted significance level of 0.05 using Fisher's exact test. TME differences between the primary RCC, BM and ECM were assessed by therapeutic target gene expression using Mann-Whitney U test, gene set enrichment analysis (GSEA) by normalized enrichment scores (NES) and false discovery rates (FDR), and a gene expression-based score reflecting HIF1-associated metabolic and stress-response pathways. **Results:** The cohort consisted of 1,775 primary, 138 BM, and 2,000 ECM. Median age was different in BM vs ECM vs primary (64 vs 66 vs 63 y, $p < 0.0001$). Approximately 75% of BM patients had not received any systemic or radiation therapy prior to tissue collection. The rwOS was 49.4 months for primary, and 30.3 months for both BM and ECM (BM vs. ECM: HR=0.96, 95%CI: 0.76-1.22, $p = 0.796$). Genomic profiling revealed, in BM compared with primary tumors, *CDKN2B* deletions (41% vs. 18.1%, $p < 0.0001$), as well as *PTEN* (22.5% vs 6.7%, $p < 0.0001$), and *TP53* mutations (22.7% vs 11%, $p = 0.0088$). Gene expression analysis demonstrated no significant differences in the expression of RCC novel therapeutic targets, including *CD70*, *ENPP3*, *CA9*, *HLA-G*, *CDH6* and *FOLH1*, between BM and primary ($p > 0.05$). Compared to primary, GSEA revealed BM were enriched in pathways including epithelial-mesenchymal transition (NES=3.41, FDR<0.001), mTORC1 signaling (NES=3.05, FDR=0.002), hypoxia (NES=2.68, FDR=0.009), and others. Compared to ECM, BM showed hypoxia enrichment (NES=2.90, FDR=0.023), while ECM was enriched in mitotic spindle (NES=-3.84, FDR<0.0001) and G2M checkpoints (NES=-3.32, FDR<0.0001). The HIF1-associated hypoxia score was significantly higher in BM vs primary ($p < 0.01$). **Conclusions:** Conserved expression of multiple actionable RCC therapeutic targets across primary and BM sites supports the biological feasibility of emerging targeted and immune-based therapies in CNS disease. The findings provide a biologic framework for understanding RCC BM and highlight hypoxia-associated pathways. Key limitations include the use of tissue-based rather than clinically adjudicated BM definitions, and the lack of cancer stage information. Research Sponsor: None.

Central nervous system metastases in hereditary breast cancer according to germline pathogenic variants: A real-world cohort study.

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Background: Hereditary breast cancer (HBC) accounts for approximately 5–10% of cases and involves pathogenic germline variants (PGVs) beyond *BRCA1/2*. While metastatic patterns differ by tumor subtype, data on central nervous system (CNS) metastases according to germline genetics remain scarce. We evaluated the incidence, clinical characteristics and survival outcomes of CNS metastases in metastatic according to PGV subgroup. **Methods:** A cohort retrospective study included patients aged ≥ 18 years with invasive or microinvasive breast cancer and confirmed PGVs treated between 2019 and 2025 at A.C. Camargo Cancer Center. Clinical, histopathologic, and molecular data were analyzed in R. Associations were assessed using chi-square or Kruskal–Wallis tests. Survival outcomes were estimated by Kaplan–Meier. CNS-related progression-free survival (CNS-PFS) was defined from treatment initiation after CNS metastasis to intracranial progression or death. Overall survival after CNS metastasis (OS post-CNS) was defined from CNS metastasis to death. Median survival times with 95% confidence intervals (CIs) were reported. **Results:** Among 1,353 individuals evaluated, 463 patients with pathogenic germline variants (PGVs) were included. Median age at diagnosis was 43.7 years, and 99.6% were women. The most frequent PGVs were *BRCA1* (32.0%), *BRCA2* (22.2%), and *TP53* (12.1%). *BRCA1* carriers were diagnosed earlier than other genotypes ($p = 0.0005$). CNS metastases occurred in 21 patients (4.5%), mainly among *BRCA*-associated PGVs and *TP53*, with additional cases in *PALB2*, *ATM*, and *RAD*-related variants; none occurred in *CHEK2*, *FANCA*, or Lynch-associated variants. CNS involvement was mainly parenchymal-only (71.4%), with meningeal-only (19.0%) or combined disease (9.5%). Lesions were supratentorial-only in 47.1% and both supra- and infratentorial in 47.1%. Diagnosis was symptom-driven in 70.0%. Single CNS metastasis occurred in 38.9%, and local therapy alone was most commonly used (66.7%). No statistically significant differences in CNS metastatic patterns were observed across PGV subgroups ($p > 0.05$). Median OS after CNS diagnosis was 14 months (95% CI, 5–NR), and median CNS-PFS was 17 months (95% CI, 7–NR). **Conclusions:** In metastatic HBC, CNS metastases are uncommon but preferentially occur among patients harboring *BRCA*-associated and *TP53* pathogenic germline variants. Germline genetics may contribute to distinct metastatic phenotypes and support risk-adapted CNS surveillance strategies and therapeutic strategies in metastatic HBC. Research Sponsor: None.

Continued CNS-penetrant TKI therapy with or without local CNS therapy after brain metastasis diagnosis in NSCLC.

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Background: Patients with oncogene-driven metastatic non-small cell lung cancer (NSCLC) treated with CNS-penetrant tyrosine kinase inhibitors (TKIs) frequently develop brain metastases (BM) while continuing targeted therapy, and outcomes of adding local CNS-directed therapy in this setting are not well defined. We evaluated outcomes associated with local CNS therapy after post-TKI BM diagnosis. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network. Adults with NSCLC treated with osimertinib or lorlatinib who subsequently had a coded diagnosis of BM (ICD-10 C79.31) at least 1 month after TKI initiation and evidence of continued TKI use were included. Patients were stratified by receipt of CNS-directed local therapy (SRS/SBRT or neurosurgery) within 3 months of the index BM diagnosis versus no local therapy. The primary outcome was all-cause mortality within 180 days of the index event. Secondary outcomes included hospitalization and systemic corticosteroid use. Cohorts were balanced using 1:1 propensity score matching on demographics, comorbidities, extracranial disease, laboratory values, and TKI exposure. Survival analyses were performed, and proportional hazards assumptions were validated using Schoenfeld residuals ($p > 0.05$). **Results:** Among 1,157 eligible patients, 1,053 matched pairs were generated. Within 180 days of the index brain metastasis diagnosis, mortality was lower among patients who received local CNS therapy compared with those who did not (10.9% vs 18.1%), corresponding to a hazard ratio (HR) for death of 0.54 (95% CI 0.43–0.68; $p < 0.001$). Survival probabilities at 180 days were 88.7% in the local therapy cohort and 80.2% in the no local therapy cohort. Hospitalization within 180 days occurred in 20.3% of patients receiving local therapy and 22.4% of those without local therapy ($p = 0.24$), with a nonsignificant trend toward delayed hospitalization (HR 0.84, 95% CI 0.69–1.01). Systemic corticosteroid use was common and similar between groups (61.3% vs 59.4%; $p = 0.40$), with no significant difference in time to steroid initiation. In an osimertinib-only sensitivity analysis, 180-day mortality was 10.5% among patients receiving local CNS therapy compared with 19.4% among those without local therapy (HR 0.48, 95% CI 0.37–0.61; $p < 0.001$). **Conclusions:** In this multi-institutional real-world cohort of patients with NSCLC receiving osimertinib or lorlatinib who developed BM, receipt of local CNS-directed therapy within 3 months was associated with lower 6-month mortality compared with continuation of targeted therapy alone, with consistent findings in an osimertinib-only sensitivity analysis. These results suggest a potential survival benefit of local CNS intervention in selected patients, while acknowledging residual confounding related to intracranial disease burden and clinical indication. Research Sponsor: None.

Intrathecal (IT) therapy–associated pseudoprogression (PsP) in leptomeningeal metastases (LM) from solid tumors.

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Background: Intracranial PsP following systemic immunotherapy has been recognized. IT therapy is a cornerstone of LM management, and prior studies support the safety and feasibility of IT immunotherapy. The occurrence of PsP specifically after IT immunotherapy for LM remains unreported. This study aims to characterize the clinical and proteomic profile of IT therapy–associated PsP (IT–PsP). **Methods:** This prospective case series consecutively enrolled LM patients receiving IT therapy between February 2024 and January 2026. Patients were treated with IT pemetrexed (PM) alone or combined with immunotherapy (PD–1 inhibitors, PD–1/CTLA–4, or PD–1/VEGF antibodies). Treatment response was assessed per RANO–LM criteria. Based on the iRANO criteria, IT–PsP was considered as radiographic progression without significant worsening of LM–related symptoms or neurological deficits. Furthermore, patients were defined as IT–PsP only if they also met at least one of the following criteria without salvage LM–directed therapy: sustained conversion of cerebrospinal fluid (CSF) cytology to negative, subsequent neuroimaging improvement, or absence of progressive neurological symptoms/signs with stable disease for ≥ 3 months. CSF proteomics was analyzed via Olink Target 96 Immuno–Oncology panel. **Results:** Of 144 enrolled patients, 75 received IT PM and 69 received IT immunotherapy plus PM. IT–PsP was identified in 12 patients (8.3%). Median age was 53.5 years (range 30–66) and 10 were female. Primary tumors were lung adenocarcinoma (n=11) and breast cancer (n=1). None received concurrent systemic immunotherapy. The median time to PsP occurrence was 5.2 months (range 1.5–12) after the first IT treatment. PsP incidence was significantly higher in the combination group (15.9%, 11/69) than with IT PM alone (1.3%, 1/75) ($P=0.002$). 6 (50%) achieved sustained conversion to negative CSF cytology. Radiographically, lesions improved in 7 patients (58.3%) and remained stable in 2 (16.7%). All PsP patients were followed up for a median of 7.1 months (range 1–13.6) with no neurological progression. Median overall survival from enrollment and from PsP onset were not reached. CSF proteomic profiling revealed that IT–PsP samples, compared to both progressive LM and pre–treatment samples, showed significant downregulation of tumor–associated proteins (CCL20, LAP TGF–beta–1, IL8, CCL4). Furthermore, compared to post–treatment response samples, IT–PsP was associated with significant upregulation of inflammatory markers, including Gal–9, IL15, and ADA. **Conclusions:** This study characterizes the clinical features and distinct CSF proteomic signature of IT–PsP in LM. The significantly higher PsP incidence with IT immunotherapy underscores that, in the immunotherapy era, relying exclusively on neuroimaging to define LM progression necessitates careful re–evaluation. Research Sponsor: Huizhou Science and Technology Innovation Team Project; 2023EQ050012; Huizhou Outstanding Young Scientific and Technological Talents Program; 2025EQ050018.

Outcomes of CD-19–directed CAR-T therapy in patients with primary and secondary central nervous system lymphoma: A multi-center observational study.

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Background: CD-19 directed chimeric antigen receptor T-Cell (CAR-T) therapies have been approved for the treatment of diffuse large B-Cell lymphoma; however, patients with primary central nervous system (CNS) lymphoma were excluded from pivotal registration trials. Although early-phase trials and meta-analysis suggest promising efficacy in CNS lymphoma, existing data remain limited by small sample sizes. We conducted a large, multicenter observational study evaluating outcomes of CD19–directed CAR-T therapy in patients with primary or secondary CNS lymphoma. **Methods:** This study utilized the TriNetX database, encompassing over 110 healthcare organizations, to evaluate outcomes of adults with a diagnosis of primary or secondary CNS lymphoma prior to receiving CAR T therapy between 2019 and 2025. Outcomes were assessed from the time of CAR-T infusion. The outcomes analyzed were 1-year overall survival, as well as development of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), treatment with tocilizumab, and risk of infection within 100 days post-CAR-T infusion. Kaplan–Meier estimated event rates were used to assess the primary outcomes. **Results:** We identified 155 patients with a diagnosis of primary or secondary lymphoma who received CD-19 directed CAR-T therapy. The median age at CAR-T infusion was 63 years. The cohort was predominately male (57%) and white (87%). A majority of the cohort, 80%, received Fludarabine/ Cyclophosphamide for lymphodepletion chemotherapy; 16% received Bendamustine. Most patients received axicabtagene ciloleucel (n=78), followed by lisocabtagene maraleucel (n=56), and tisagenlecleucel (n=21). The Kaplan–Meier estimated overall survival at one and three years was 63.9% and 46.9%, respectively. The estimated cumulative risk for CRS and ICANS post-CAR-T infusion was 58.7% and 26.5% respectively – 49.0% were treated with tocilizumab. The risk of infection by day 100 post-CAR-T infusion was 43.2%. **Conclusions:** CNS lymphomas have been associated with limited overall survival and represent an unmet need, necessitating the emergence of new therapeutic strategies. Our findings support the efficacy and safety of CAR-T in this population. To our knowledge, this is the largest single observational study of patients with CNS lymphoma treated with CAR-T. Research Sponsor: None.

Outcome	Time Point	Rate (%) (n = 155)
Overall Survival	1 years	63.9%
	3 years	46.9%
CRS	60 days	58.7%
ICANS	60 days	26.5%
Tocilizumab Use	60 days	49.0%
Any Infection	100 days	43.2%

The association of economic measures and patient outcomes with geographical disparities in access to a UCNS board-certified neuro-oncologist in the United States.

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Background: Neuro-oncology is increasingly centralized in academic tertiary centers, potentially creating geographic and economic inequality. This study aims to quantify the national distribution of neuro-oncologists in the United States and evaluate the association between regional economic capacity, metropolitan urbanicity, and population-level clinical outcomes. **Methods:** We conducted a nationwide cross-sectional ecological analysis using 2025 United Council for Neurologic Subspecialties (UCNS) data, US Bureau of Economic Analysis state-level GDP, and US Census Bureau demographics. Spatial accessibility was modelled for US counties using geodesic distance from population centroids. Outcome measures included CNS tumor mortality and Disability-Adjusted Life Years (DALYs). **Results:** We identified 323 UCNS board-certified neuro-oncologists distributed across 70 Metropolitan Statistical Areas (MSAs). Work-force distribution was strongly associated with state-level economic magnitude ($r=0.930$ [95% CI: 0.878–0.960], $p<0.0001$), with gross domestic product (GDP) explaining 86.4% of variance ($R^2=0.864$). Critically, economic intensity independent of state population was a significant driver, with GDP per capita correlating with specialist density ($r=0.344$, $p=0.014$). Specialists were located exclusively within MSAs ($\chi^2 = 52.28$, $p < 0.0001$), however 81.9% of MSAs lacked local subspecialty presence. Spatial analysis revealed 45.4% of the US population has local access (<20 miles), while 16.5% (55.2 million Americans) live in "Care Deserts" greater than 100 miles from the nearest neuro-oncologist. Increased specialist density predicted lower mortality rates for pediatric ($\rho = -0.34$ [95% CI: -0.56 to -0.07], $p = 0.015$) and adult ($\rho = -0.352$ [95% CI: -0.57 to -0.08], $p = 0.011$) groups. Similar inverse associations were observed for DALYs in both pediatric ($\rho = -0.339$ [95% CI: -0.57 to -0.07], $p = 0.015$) and adult ($\rho = -0.347$ [95% CI: -0.57 to -0.08], $p = 0.013$) populations. **Conclusions:** Distribution of UCNS board-certified neuro-oncologists in the United States is primarily governed by state-level economic prosperity and is critically concentrated in select metropolitan centers. This geographical concentration leaves over 80% of US metro areas without access to a UCNS board-certified neuro-oncologist. Furthermore, higher density of UCNS-certified specialists is significantly associated with reduced mortality and disease burden, suggesting that expanding this work-force may be a lever for improving population-level neuro-oncologic outcomes. Research Sponsor: None.

Use of knowledge-distilled EfficientNet to enable rapid, scalable glioma diagnosis.

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Background: Accurate preoperative classification of gliomas on MRI according to WHO 2021 integrated diagnosis is essential for surgical planning and treatment selection, yet conventional interpretation remains vulnerable to inter-observer variability. Deep learning shows promise for brain tumor classification but computational demands restrict deployment in resource-limited settings. Knowledge distillation, transferring discriminative knowledge from computationally intensive "mentor" networks to efficient "mentee" models, enables scalable AI systems maintaining diagnostic accuracy while enabling global translation. **Methods:** We analyzed 2,840 brain MRI studies sourced from six continents comprising gliomas (n=1,400; 700 WHO grade 2–3, 700 grade 4), meningiomas (n=900), and pituitary adenomas (n=540). Ground truth followed WHO 2021 integrated diagnosis with expert neuroradiologist consensus. Data were partitioned at the patient level with site-held-out external testing. A high-capacity EfficientNetB7 mentor model was developed using multi-sequence MRI inputs (T1, T2, FLAIR, post-contrast T1) and distilled into lightweight EfficientNetBo. Knowledge distillation preserved discriminative performance while enabling CPU deployment without GPU acceleration. Training: input 224×224 pixels, Adam optimizer (lr=0.001), Kullback-Leibler divergence loss (temperature T=4), twelve epochs. Performance metrics included accuracy, sensitivity, specificity, F1-score, and AUROC. Independent clinical feasibility involved 52 board-certified neuroradiologists across 11 geopolitical regions. **Results:** For WHO grade 2–3 versus grade 4 stratification, distilled EfficientNetBo achieved 97.2% accuracy, 98.1% sensitivity, 96.3% specificity, and AUROC 0.993. Differential diagnosis accuracy: 95.3% (glioma vs. meningioma), 96.1% (glioma vs. pituitary). Site-held-out external validation showed consistent performance (93–97% grading, 94–96% differential). Mean inference time: 0.19 seconds on CPU. Distilled model: 3.9 million parameters (97% reduction), 2.1 billion FLOPs (94% reduction). Neuroradiologist assessment: 94.7% rated system valuable for diagnostic confidence and surgical triage. Inter-rater agreement: 96.8% ($\kappa=0.951$, 95% CI 0.941–0.961). **Conclusions:** Knowledge-distilled EfficientNetBo achieves 97.2% accuracy for glioma grading and 95–96% for differential diagnosis while reducing parameters by 97% and enabling CPU deployment. Global validation across six continents and clinical assessment by 52 neuroradiologists establish real-world feasibility. The architecture supports translation as a decision-support tool for preoperative glioma stratification, particularly in resource-constrained settings. Prospective clinical trials evaluating impact on surgical decision-making are warranted. Research Sponsor: None.

Phase 1, first-in-human (FIH) study evaluating safety and efficacy of ABBV-706: Results from patients with high-grade central nervous system (CNS) tumors.

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Background: Patients (pts) with primary high-grade CNS tumors, especially those with glioblastoma (GBM), face poor clinical outcomes (GBM 5yr OS 5–10%). Seizure-related 6 homolog (SEZ6) is overexpressed in many tumor types, including primary CNS tumors. ABBV-706 is a SEZ6-targeting antibody-drug conjugate with topoisomerase 1-inhibitor payload that has shown a manageable safety profile in pts with small cell lung cancer. We present safety and efficacy data from a phase 1, FIH study evaluating ABBV-706 in pts with CNS tumors. **Methods:** This phase 1, FIH study (NCT05599984) enrolled pts ≥ 18 years with histologically/cytologically confirmed advanced relapsed/refractory GBM (IDH-wildtype, Grade [G] 4) or astrocytoma (IDH-mutant, G 3/4). Pts had ECOG performance score ≤ 1 , and ≥ 1 measurable lesion per Response Assessment in Neuro-Oncology (RANO). Pts had prior surgical resection and progressed after receiving standard of care treatment. During dose escalation and expansion, pts received 1.3–3.5 mg/kg and 2.5 mg/kg ABBV-706, respectively. Treatment was every 3 weeks until disease progression or intolerable toxicity. Endpoints included safety and efficacy determined by RANO criteria. **Results:** As of Sep 27, 2025, 48 pts with primary CNS tumors (GBM, n=41; astrocytoma, n=6; missing indication, n=1) received ABBV-706 (1.3 mg/kg, n=1; 2.5 mg/kg, n=44; 3.0 mg/kg, n=1; 3.5 mg/kg, n=2). Among all pts, median age was 50 years (range 18–78), 58% were male, and the median number of prior lines of therapy was 2 (range 1–5). Median follow-up was 13.7 and 13.2 months for pts with GBM and astrocytoma, respectively. Treatment-related adverse events (TRAEs) were observed in 90% of pts. Most common toxicities were hematological (65%) and gastrointestinal (52%) events. G ≥ 3 TRAEs were observed in 60% of pts; most commonly anemia (40%). TRAEs led to treatment discontinuation, dose interruption, and dose reduction in 4%, 38%, and 27% of pts, respectively. No G 5 TRAEs were reported. One pt had pneumonitis (2.5 mg/kg, G 2). Among all pts, ORR was 8%, and 2 pts (4%) had a confirmed complete response. Efficacy data for GBM are shown in the Table. SEZ6 IHC expression was similar between GBM pts with (n=4) and without (n=31) an objective response. **Conclusions:** In pts with previously treated primary CNS tumors, ABBV-706 had a comparable safety profile to that observed in other tumors and showed encouraging antitumor activity. Clinical trial information: NCT05599984. Research Sponsor: AbbVie Inc.

Efficacy of ABBV-706.^a

	Pts with GBM 2.5 mg/kg ABBV-706 (n=41)
BOR, n (%)	
CR ^b	2 (5)
PR ^b	4 (10)
SD	21 (51)
PD ^b	9 (22)
NE/not assessed	5 (12)
ORR ^c , n (%), 95% CI	4 (10), 3–23
CBR, n (%), 95% CI	
>5 weeks	26 (63), 47–78
>6 months	5 (12), 4–26
Median PFS, months (95% CI)	2.7 (2.3–5.4)
Probability at 9 months, % (95% CI)	10 (3–24)
Median OS, months (95% CI)	6.4 (5.4–8.3)
Probability at 12 months, % (95% CI)	17 (6–33)

^aBy investigator per RANO.

^bIncluding confirmed + preliminary.

^cConfirmed.

Initial analysis of adoptive neoantigen-specific T-cell immunotherapy for MGMT-unmethylated glioblastoma (TVI-AST-008): Signals amid control arm attrition.

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Background: MGMT-unmethylated (MGMT-u) glioblastoma (GBM) confers resistance to alkylating agents and poor overall survival (OS). Limited options beyond Standard of Care (SOC) drive patient pursuit of experimental therapies, complicating randomized controlled trials (RCTs). TVI-AST-008 evaluates safety and efficacy of adding autologous neoantigen-specific T-cell immunotherapy to SOC in this high-risk population. **Methods:** In this prospective RCT, newly diagnosed MGMT-u GBM patients were randomized 1:1 post-resection to Immunotherapy + SOC or SOC alone, stratified by age, residual tumor, and sex. The investigational arm used patient tissue to manufacture an autologous vaccine and undergo tumor cell vaccination to induce antigen-specific priming. Following leukapheresis, harvested lymphocytes undergo *ex vivo* T-cell activation/expansion (TVAX). On completion of SOC (radiation/temozolomide), manufactured cells undergo adoptive transfer with low-dose IL-2. Primary endpoint: OS. **Results:** As of September 2025, 21 subjects (median age 60) were randomized: Treatment (n=11) or Control (n=10). Control arm retention was challenging: 4/10 withdrew post-randomization to pursue other experimental therapies, leaving 6 evaluable Controls. Six Treatment subjects completed infusion. Despite limited statistical power, survival divergence emerged: mean OS for Controls (n=6) was 6.6 months versus 10.6 months for infused Treatment patients (n=6), with survivors followed at a median of 14 months (2 died at 9 and 10 months). Safety was favorable; adverse events were Grade 1–2 (pyrexia, rash) consistent with immune activation. No SAEs attributed to the investigational product. **Conclusions:** Early TVI-AST-008 data suggest adoptive neoantigen-specific immunotherapy is feasible, safe, and early signals suggest possible improved survival in MGMT-u GBM. High post-randomization withdrawal in Controls highlights challenges of SOC-controlled trials in this setting. Future validation may require synthetic controls or crossover allowances to ensure trial viability. Clinical trial information: NCT05685004. Research Sponsor: FDA/HHS; R01FD007259.

Impact of vorasidenib vs placebo on seizure rates and quality of life: Exploratory analysis from the phase 3 INDIGO study.

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Background: Grade 2 diffuse gliomas with isocitrate dehydrogenase 1/2 mutations (mIDH1/2) are incurable brain tumors with poor long-term prognosis and tumor-related symptoms, eg seizures, that negatively impact patients' (pts) quality of life (QoL). Vorasidenib (VOR) is an oral, brain-penetrant, dual inhibitor of mIDH1/2 approved in >40 countries for treating grade 2 mIDH1/2 gliomas following the positive clinical outcomes, including tumor volume reduction, shown in the Phase 3 INDIGO study (NCT04164901). We investigated the effect of long-term VOR treatment on seizure activity and QoL in pts with mIDH1/2 glioma in INDIGO. **Methods:** Pts aged ≥ 12 years with grade 2 mIDH1/2 glioma, no prior glioma treatment other than surgery and with controlled seizures were randomized 1:1 to receive VOR 40 mg or placebo (PBO) daily. Data from the pre- and post-unblinding periods were used; PBO pts after crossover were excluded from the analyses. Exploratory analyses for the number of on-treatment seizures were conducted in pts with ≥ 1 seizure in the baseline or on-treatment periods using a negative binomial regression model. Seizure severity was self-reported (1 [not bad] to 10 [as bad as imaginable]). QoL was measured using the Functional Assessment of Cancer Therapy – Brain (FACT-Br) scale and FACT-Br brain cancer subscale (BrCS), and changes were estimated with time-to-event analysis. **Results:** During the study, 110/331 pts (33.2%) reported ≥ 1 seizure (VOR n=55; PBO n=55). VOR treatment showed a constant and sustained effect on seizure control, reflected by significantly lower seizure rates per person per year than in the PBO group (Table), and lower number and severity of seizures over time. In addition, in pts with a seizure burden (≥ 1 seizure), VOR significantly delayed time to first worsening of FACT-Br and FACT-Br BrCS scores (hazard ratio [95% confidence interval]: FACT-Br, 0.38 [0.15, 1.00], $P=0.0435$; FACT-Br BrCS, 0.32 [0.11, 0.91], $P=0.0263$). **Conclusions:** In pts with mIDH glioma and ≥ 1 on-study seizure, long-term VOR treatment generally led to a sustained decrease in seizure activity and severity and delayed worsening of QoL. These results suggest that VOR may have an additional benefit on QoL in pts who experience seizures. Clinical trial information: NCT04164901. Research Sponsor: Servier.

Exploratory analyses of VOR treatment and seizure rate in pts who reported ≥ 1 seizure in the baseline or on-treatment periods in INDIGO.

	VOR (n = 56)	PBO (n = 56)
Patients with ≥ 1 on-treatment seizure, n (%)	55 (98.2)	55 (98.2)
Rate of on-treatment seizures per person-year* (95% CI)	13.2 (5.8, 29.8)	64.9 (26.5, 159.1)
Ratio of rates: VOR vs PBO (95% CI)	0.20 (0.08, 0.52)	
Two-sided P value [†]	0.0008	

*Estimated using negative binomial regression model adjusted by number of seizures and tumor size at baseline.

[†]Not prespecified and not adjusted for multiplicity; should be interpreted with caution. Data cut-off: January 17, 2025. CI, confidence interval; PBO, placebo; VOR, vorasidenib.

Tumor treating fields therapy in patients with newly diagnosed glioblastoma and poor performance status: Real-world analysis of patients treated in the US.

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Background: TTFields therapy is an FDA-approved treatment for patients with newly diagnosed glioblastoma, showing benefit in overall survival (OS) when added to maintenance temozolomide (TMZ). While device effectiveness was demonstrated regardless of performance status (PS) in the EF-14 study, only patients with Karnofsky Performance Status (KPS) of ≥ 70 were eligible for the study. This study investigates real-world outcomes of patients with newly diagnosed glioblastoma and poor PS who were treated with TTFields. **Methods:** Electronic medical records of patients initiating treatment with TTFields in the US commercial setting between January 1, 2019 and December 31, 2021 were accessed via the xCures real-world data platform and Novocure systems, from which clinical data were extracted. To be included in the analysis, patients needed to have a documented new diagnosis of glioblastoma occurring within 180 days of initiating TTFields and have KPS ≤ 60 or ECOG PS ≥ 2 within 3 weeks of treatment initiation. IDH status was ascertained where data were available. Device usage was calculated as the average percentage of time the device was used within the first 3 months of therapy, as recorded by the device log files. Patients were divided into high and low usage groups. High usage was defined as usage $\geq 50\%$ and treatment duration ≥ 30 days, and low usage as usage $< 50\%$ or treatment duration < 30 days, excluding patients with a death event within 30 days of initiating TTFields. Demographics, disease characteristics, and survival outcomes were evaluated. Data cutoff for analysis was Jan 7, 2026. **Results:** The study included 306 patients, of whom 198 (65%) were high users and 108 (35%) low users. Baseline characteristics were balanced between the two groups. Although most patients had KPS of 60 or ECOG PS of 2 (n=204, 67%), the study included 102 patients (33%) who had KPS ≤ 50 or ECOG PS ≥ 3 . The entire cohort had median OS from diagnosis of 13.3 months (95% CI, 12.4–14.5). Median OS was 14.1 months (95% CI, 12.8–15.9) in the high-use group compared with 11.9 months (95% CI, 9.6–13.3) in the low-use group (HR, 0.69 [95% CI, 0.53–0.89]; $P=0.005$). Similar results were observed regardless of the performance scale utilized. Further subgroup analysis showed a consistent usage effect for patients ≥ 65 and < 65 years of age (HR, 0.71 [0.49–1.02], $P=0.067$ and HR, 0.69 [0.47–1.00], $P=0.049$, respectively). **Conclusions:** Patients with newly diagnosed glioblastoma and poor performance status receiving TTFields therapy in the real-world setting appear to have favorable survival when compared with historical data. Usage is associated with improved survival in this population, including among elderly patients for whom treatment options are limited. Additional studies examining TTFields in this high-need population with limited trial options are warranted. Research Sponsor: None.

Beyond survival: Longitudinal prognostication in glioblastoma using conditional survival—A population-based study.

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Background: Glioblastoma multiforme (GBM) carries a poor prognosis, and the initial survival projections provided at diagnosis do not accurately depict the evolving risk that exists for all GBM survivors. Conditional survival (CS), defined as the probability of surviving an additional period after having lived to a specific time point, provides a much more accurate way of defining prognosis for these patients. We evaluated conditional survival patterns in a large population-based cohort of patients with glioblastoma. **Methods:** Adult patients who were diagnosed with primary glioblastoma between 2000 and 2022 were identified from the SEER 17 Registries. The estimated overall survival (OS) was determined by using the Kaplan-Meier method. We also calculated one year and two-year conditional survival (CS) probabilities at multiple landmark times (0–24 months). In addition, we stratified the conditional survival by the status of surgical resection and whether or not the patient received radiation therapy. **Results:** There were 52,125 patients in our sample. As expected, the median OS was very poor, dropping from 37.3% at 12 months to 16.0% at 24 months. Nevertheless, the conditional survival was significantly better than overall survival. One-year CS increased from 40.4% at diagnosis to 57.2% among patients surviving 24 months, while two-year CS improved from 17.3% to 39.4% over the same landmarks. Patients who underwent surgical resection had higher early CS compared with biopsy or no surgery, though differences diminished at later landmarks. Similar trends were found in CS rates in patients who received radiation therapy, indicating survivorship selection over time as opposed to a decrease in the effectiveness of treatments. **Conclusions:** Conditional survival in glioblastoma improves markedly with increased time of survival. Therefore, it is essential to use CS in place of traditional survival statistics to provide more accurate prognoses for glioblastoma patients. Research Sponsor: None.

Landmark Time (Months)	Overall Survival	1-Year Conditional Survival	2-Year Conditional Survival	1-Year CS (Resection)	1-Year CS (No resection/ Biopsy)	1-Year CS (RT Yes)	1-Year CS (RT No/Unknown)
0	92.4%	40.4%	17.3%	46.7%	17.1%	48.7%	14.1%
6	56.3%	42.0%	20.9%	43.2%	32.3%	42.5%	37.9%
12	37.3%	42.9%	24.5%	43.1%	40.7%	42.4%	47.9%
18	23.7%	49.8%	31.7%	49.9%	48.7%	49.2%	56.0%
24	16.0%	57.2%	39.4%	57.1%	57.2%	56.5%	63.2%

RT: Radiotherapy.

A phase I study to assess the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of KH617 for patients with advanced solid tumors (including diffuse gliomas of adulthood).

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Background: Outcomes in patients (pts) with recurrent glioblastoma (rGBM) are poor, with historical median overall survival (mOS) of 7–8 months. KH617 is a sesquiterpene compound that exhibits a wide spectrum of anti-cancer properties, has low toxicity, and is capable of traversing the blood-brain barrier. It can inhibit the growth, proliferation, and migration of tumors via multiple mechanisms, mitigate the malignant phenotype of tumor cells, and facilitate the transdifferentiation of tumor cells into normal cells. This is a phase I study of KH617 in pts with advanced solid tumors (including diffuse gliomas of adulthood). Here, we report the results of the dose escalation stage. **Methods:** Pts with histologically confirmed advanced solid tumors (including diffuse gliomas of adulthood) that were no longer responding to standard therapies were enrolled. The Bayesian Optimal Interval (BOIN) design was used for dose escalation, having explored in 7 successive cohorts (5–60mg/kg). **Results:** As of Dec, 30 2025, 32 pts were enrolled across 7 dose levels, including 23 pts with rGBM, 7 with non-glioblastoma, and 1 each with adenocarcinoma and spinal cord ependymoma. The median age was 51 years, and 19 (59.4%) pts were male. No dose-limiting toxicity (DLT) or treatment-related serious adverse events (TRSAEs) were observed, and the maximum tolerated dose (MTD) was not reached. The most frequently reported ($\geq 10\%$) treatment-related serious adverse events (TRAEs) were white blood cell count decreased, neutrophil count decreased, lymphocyte count decreased, abnormal ECG T wave, and sinus bradycardia. Only 1(3.13%) pt reported grade ≥ 3 adverse event. Efficacy signals were observed especially in the 23 rGBM pts, who were administered KH617 across 7 doses (n = 1, 1, 3, 2, 8, 7, 1 in 5, 10, 17, 25, 33, 45, 60mg/kg cohorts, respectively), the mOS was 16.07 months. At the recommended phase 2 dose (RP2D) of 33mg/kg, 8 rGBM pts were included in the efficacy evaluation, objective response rate (ORR) was 12.5%, median progression-free survival (PFS) was 1.84 months, mOS exceeded 21 months (3 died and 5 were still alive). In the pharmacokinetic (PK) study, C_{max} no longer increased with escalating doses from 25 mg/kg to 45 mg/kg, indicating that the peak plasma concentration had already reached the maximum plateau level under the current dosing. Combined the efficacy data with the PK data, 33 mg/kg was confirmed as the RP2D. **Conclusions:** KH617 has shown significantly superior anti-tumor activity compared to the historical mOS in pts with rGBM, while also being well-tolerated. Clinical trial information: CTR20223286. Research Sponsor: Sichuan Honghe Biotechnology Co., Ltd.

Interrupting HEG1/Cx43 interaction to promote cuproptosis via inhibiting gap junction to overcome glioblastoma radioresistance.

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Background: Glioblastoma (GBM) is the most common and aggressive primary malignant tumor of the central nervous system. Its intrinsic radioresistance leads to suboptimal therapeutic outcomes. A prior clinical trial by our team revealed that mutations in the *HEG1* gene lead to upregulated protein expression, a key factor limiting the benefit from standard radiotherapy in GBM patients. As a form of non-classical programmed cell death induced by radiotherapy, we hypothesized that high HEG1 expression reduces the susceptibility of GBM cells to cuproptosis, thereby promoting radiotherapy resistance. **Methods:** Cellular functional assays were performed to evaluate the impact of HEG1 expression on cuproptosis sensitivity and radiotherapy response in GBM cells. Molecular techniques were used to assess intracellular and intercellular copper ion flow. Co-immunoprecipitation and inhibition of protein degradation pathways were employed to investigate the direct interaction between HEG1 and the gap junction protein Connexin 43 (Cx43), and its inhibitory effect on Cx43 degradation via the endolysosomal pathway. Structural modeling combined with virtual screening of a drug library was conducted to identify potential compounds disrupting the HEG1-Cx43 interaction. Site-directed mutagenesis and kinase activity modulation were used to elucidate the mechanism by which c-Kit kinase promotes HEG1-Cx43 binding by phosphorylating HEG1 at tyrosine residue Y1350. Functional validation was performed both in vitro and in vivo using GBM models. **Results:** High HEG1 expression facilitated intercellular copper ion flow, dampened intracellular copper ion fluctuations, and consequently blocked the propagation of cuproptosis. Mechanistically, HEG1 directly interacted with Cx43, inhibiting its degradation via the endolysosomal pathway and sustaining gap junction establishment. Virtual screening identified several multi-target tyrosine kinase inhibitors capable of disrupting the HEG1-Cx43 interaction. Mechanistic studies revealed that c-Kit kinase promoted this interaction by phosphorylating HEG1 at Y1350. Both in vitro and in vivo functional validation demonstrated that targeting the HEG1-Cx43 interaction reactivated cuproptosis and sensitized GBM to radiotherapy. **Conclusions:** Our findings elucidate the regulatory role of the "HEG1-Cx43-cuproptosis" axis in GBM radioresistance, offering new insights for treatment. The combination of multi-target tyrosine kinase inhibitors and cuproptosis inducers may represent a promising novel therapeutic strategy for GBM. Research Sponsor: National Key R&D Program of China; Natural Science Foundation of China; Cancer Innovative Research Program of Sun Yat-sen University Cancer Center; Natural Science Foundation of Guangdong Province; Young Talents Program of Sun Yat-sen University Cancer Center; Guangzhou Science and Technology Plan; Guangzhou Basic and Applied Basic Research Foundation.

Histopathology-verified comparison of FET PET and contrast-enhanced MRI for tumor visualization in glioblastoma.

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Background: In glioblastoma, precise visualization is a prerequisite for optimal resection strategies and accurate radiotherapy volume definition. In routine practice, contrast-enhanced MRI (CE-MRI) is most commonly used; however, it can underestimate tumor extent when viable tumor is present without blood–brain barrier disruption and therefore without contrast uptake. The present study examined whether amino acid PET with O-(2-[¹⁸F] fluoroethyl)-L-tyrosine (FET) can better visualize the true distribution of tumor tissue and thereby improve preoperative assessment. **Methods:** In this prospective, biopsy-validated single-center study, in 61 patients with IDH-wildtype glioblastoma (44 newly diagnosed, 17 recurrent) 472 biopsies spatially correlated with preoperative FET PET and CE-MRI were histopathologically evaluated. Diagnostic metrics were calculated and compared between modalities using McNemar and Chi² tests ($p = 0.05$). **Results:** Overall, FET PET identified tumor tissue with significantly higher sensitivity than CE-MRI (91.2% vs. 55.7%; $p < 0.001$). When benchmarked against T2/FLAIR, FET remained more sensitive (85.3%; $p = 0.012$) while also demonstrating a pronounced gain in specificity (82.5% vs. 33.3%; $p < 0.001$). Remarkably, there was the high reliability of FET in regions without MRI contrast enhancement: biopsies taken from FET-positive areas without contrast enhancement showed a positive predictive value of 98.3%. Subgroup analyses consistently demonstrated the advantage of FET across clinical and histological strata, including newly diagnosed and recurrent disease ($p < 0.001$), as well as within cohorts with resection ($p < 0.001$; specificity $p = 0.03$) or biopsy ($p < 0.001$). Importantly, performance advantages were also observed regardless of histological tumor cell density, with FET exceeding CE-MRI in both histological strata (infiltration zone and solid tumor, both $p < 0.001$). **Conclusions:** FET PET demonstrated significant diagnostic superiority over CE-MRI for the visualization of glioblastoma tissue. Comparable positive predictive values in contrast-enhancing and non-enhancing regions indicate that FET PET detects tumor reliably, independent of the blood–brain barrier integrity. These findings support the integration of amino acid PET as an important component in target definition for both surgical and radiation planning in glioblastoma. Research Sponsor: None.

Caregiver professional employment and its impact on glioblastoma patient survival: Results from two prospective studies.

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Background: Caregiver burden is a crucial factor to consider in the diagnosis and care of patients with glioblastoma (GBM). Despite growing interest in caregiver issues, data on caregiver burden and, in particular, professional and working burden are limited, as well as the potential effect of caregiver burden on patients' survival. **Methods:** We collected caregiver data from two prospective observational studies (ISES 1 and ISES 2) investigating the impact of socioeconomic variables (SES) in GBM patients. In particular, we collected data on the presence and type of caregiver, the caregiver's professional situation, and any professional modifications after the GBM diagnosis at time of adjuvant treatment start and after six months (in patients enrolled in ISES 2 study). **Results:** Overall, 511 GBM isocitrate dehydrogenases wild-type (IDH-wt) patients were included. The median follow-up period was 55.2 months (95% CI, 44.3–86.3), and the median overall survival was 15.7 months (95% CI, 14.8–17.2). A caregiver was present for 472 patients (92.4%), consisting mainly of partners or daughters and sons. At the start of adjuvant treatment, 158 caregivers (30.9%) reduced their working hours, and 55 caregivers (10.8%) stopped working. For 232 patients, a longitudinal assessment of caregiver condition was collected, and 71 caregivers (30.6%) reduced their working hours, while 33 patients (14.2%) stopped their work activities. Patients whose caregivers were in stable employment had a longer life expectancy than those whose caregivers were not (multivariate - HR 0.76, 95% CI 0.60–0.94, $p = 0.03$), regardless of other known prognostic factors, as confirmed by a multivariate analysis (Table 1). **Conclusions:** Our study revealed that GBM diagnosis often leads to a negative impact on caregiver work activities. A stable caregiver employment translates independently to a long-life expectancy of patients with GBM, regardless of other recognized prognostic factors. Policies supporting the professional and social activities of caregivers could improve not only the quality of care for GBM patients but also their clinical outcomes. Clinical trial information: 0321-3733778. Research Sponsor: None.

VARIABLES	Univariate analyses Hazard Ratio (95%CI) p value	Multivariate analyses Hazard Ratio (95%CI) p value
MGMT		
Unmethylated vs methylated	2.23 (1.79 – 2.77) $p < 0.001$	0.43 (0.34-0.55) $p < 0.001$
SURGERY		
Biopsy	Ref	Ref
Partial resection	0.51 (0.38-0.69)	0.62 (0.43-0.88)
Complete resection	0.50 (0.37-0.69) $p < 0.001$	0.61 (0.42-0.89) $p = 0.008$
TREATMENT		
RT (40Gy)/CT ->CT vs RT (60Gy)/CT ->CT	1.31 (1.04-1.73) $p = 0.02$	1.04 (0.77-1.49) $p = 0.8$
ECOG		
0 vs 1 or more	0.67 (0.54-0.82) $p < 0.001$	0.72 (0.56-0.91) $p = 0.007$
STEROIDS		
Yes vs No	1.94 (1.57-2.40) $p < 0.001$	1.75 (1.31-2.13) $p < 0.001$
AGE		
(As continuous for year)	1.02 (1.01-1.03) $p < 0.001$	1.01 (1.0009-1.03) $p = 0.04$
CAREGIVER		
(professional condition) Employed vs other	0.73 (0.59-0.90) $p = 0.005$	0.76 (0.60-0.94) $p = 0.03$

Expression patterns of circulating microRNAs in classification models: New opportunities in brain tumor diagnosis.

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Background: Diffuse gliomas are the most common primary brain tumors and, according to the 2021 WHO classification, are divided into three main types: IDH-wild-type glioblastomas, IDH-mutant astrocytomas, and IDH-mutant oligodendrogliomas with 1p/19q codeletion. Oligodendrogliomas are neuroepithelial tumors of the central nervous system that have histological and molecular characteristics distinct from other subtypes of diffuse gliomas. The problem of early diagnosis of oligodendrogliomas, due to their location, requires the search for accessible and informative markers. Circulating microRNAs in blood plasma appear to be the most promising in this aspect. The purpose of the study was to develop a model for the diagnosis of oligodendrogliomas based on the expression profiles of microRNAs circulating in blood plasma. **Methods:** The study included 251 participants: 84 patients with glioblastomas, 51 patients with astrocytomas, 12 patients with oligodendrogliomas, 47 patients with meningiomas, 14 patients with lung cancer metastases, 25 patients with breast cancer metastases, and 18 healthy donors. The miRNeasy Serum/Plasma Kit (Qiagen, Germany) was used to isolate the microRNA fraction from blood plasma. The expression levels of hsa-miR-30c-5p, hsa-miR-186-5p, hsa-miR-194-5p, hsa-miR-484, hsa-miR-19b-3p, hsa-miR-431-5p, hsa-miR-363-3p, hsa-miR-128-3p, hsa-miR-3168, hsa-miR-192-5p, hsa-let-7c-5p, hsa-miR-340-5p, hsa-miR-182-5p and hsa-miR-144-5p were measured by stem loop RT-qPCR. **Results:** The model for diagnosing cases with oligodendrogliomas was as follows: $K_o = -1.59 \times \text{hsa-miR-128-3p} - 1.97 \times \text{hsa-miR-194-5p} + 1.78 \times \text{hsa-miR-19b-3p} - 2.47 \times \text{hsa-miR-3168} + 3.41 \times \text{hsa-let-7c-5p} + 0.91 \times \text{hsa-miR-192-5p} + 1.39 \times \text{hsa-miR-340-5p} - 1.8$, where K_o is the coefficient used to differentiate cases with oligodendrogliomas from other cases. The optimal cut-off value for K_o was 0.38 with a Youden index of 0.86. Model validation on the test dataset revealed that cases with oligodendrogliomas typically have calculated coefficient values ≥ 0.38 . ROC analysis yielded the following model metrics: sensitivity – 100%, specificity – 85.7%, accuracy – 92.9%, and AUC – 0.93. **Conclusions:** The developed model opens up new opportunities for the early diagnosis of oligodendrogliomas and may eventually become part of a test system for the differential diagnosis of brain tumors. Research Sponsor: None.

Global validation of a brain cancer liquid biopsy.

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Background: Delayed diagnosis of brain cancer leads to approximately two-thirds of patients being identified only after presentation to the emergency department with advanced symptoms or established neurological deficits. Implementation of a simple liquid biopsy test as a rule-out test prior to confirmatory imaging, could facilitate earlier and more efficient triage of patients presenting with non-specific symptoms suggestive of brain cancer, enabling prioritization for those most at-risk and accelerate diagnostic pathways. **Methods:** Presented here is the clinical validation of the Dxcover Brain Cancer Liquid Biopsy Platform obtained to support regulatory approvals. The multi-centre and observational 'Early and tiMely detection of BRAin CancEr' ('EMBRACE') study was conducted with prospective patient recruitment across seven sites in Europe. The target population consisted of patients with symptoms indicative of brain cancer. Test performance was assessed by comparison of the liquid biopsy result to diagnostic imaging. Furthermore, the liquid biopsy test was then independently tested on an additional clinical dataset obtained from a US patient population (n=234) as part of a CLIA laboratory validation study. **Results:** In the EMBRACE performance evaluation, 2554 patients were enrolled across the seven collection sites; 2324 were deemed eligible and taken forward for test assessment. There were 697 brain tumours in total, of which 395 were malignant, and 1627 non-tumour diagnoses. In the intended use population, the reported diagnostic performance was 86% sensitivity for brain cancer detection with 44% specificity, and a 99% negative predictive value (NPV). Notably, for the most prevalent and most aggressive brain cancer, glioblastoma, 86% of cases were successfully identified. Additionally, 94% of patients with central nervous system lymphoma, and 90% of brain metastases were predicted correctly as having tumours. The test has gained regulatory approval for use in the UK and in Europe, gaining UKCA and CE – IVDR certification respectively. The CLIA validation has provided additional confirmation of the clinical utility of the liquid biopsy test in the US population. **Conclusions:** Existing symptom-based referral pathways are ineffective for the detection of brain cancer, and there is an urgent need for new tests to help with clinical decision making. With a NPV of 99%, the Dxcover Liquid Biopsy test could aid with the efficient stratification of patients toward diagnostic imaging. Research Sponsor: None.

Genomic determinants of radiation necrosis in diffuse glioma patients.

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Background: Diffuse gliomas are the most common primary brain tumors, requiring multi-modal therapy. Radiotherapy (RT) represents a key pillar of treatment; however, radiation-induced brain toxicities remain a major challenge. Radiation necrosis (RN) is a delayed complication that can impair clinical outcomes and quality of life. Emerging evidence suggests that tumor biology, together with clinical factors, can influence radiation toxicity in a variety of cancer entities. However, in diffuse gliomas, tumor-intrinsic biomarkers predisposing to radiation toxicities remain poorly defined. We hypothesized that integrating clinical features with tumor genomic data could identify patients at increased risk of developing RN. **Methods:** We analyzed a cohort of 943 adult patients with diffuse gliomas treated between 2014 and 2024 at MD Anderson. All tumors were classified according to the WHO 2021 criteria into three diagnoses: GBM, astrocytoma (astro), and oligodendroglioma (OD). RN occurring at least 12 weeks after completion of RT was identified based on pathology and/or advanced brain tumor imaging (ABTI), which included conventional MRI, perfusion imaging and spectroscopy. A multivariate regression model was employed to identify clinical or genetic predictors for RN. Included covariates were demographics, diagnosis, and common genetic alterations. To address missing values, multiple imputation was utilized. **Results:** Sixty patients with RN were identified: 51 GBM (85%), 6 astro (10%), and, 3 OD (5%); compared with 883 controls: 682 GBM (77%), 140 astro (16%), and 61 OD (7%). Age, gender, and diagnoses were not associated with RN. We evaluated the top 22 altered genes and MGMT status. In the overall cohort, *IDH1* (OR 0.15 [95% CI, 0.02–0.93]; $p=0.042$) and *MDM2* (OR 0.11 [95% CI, 0.01–1.00]; $p=0.050$) alterations were associated with reduced RN risk, while *ATR* alterations were associated with increased RN risk (OR 6.05 [95% CI, 0.85–33.1]; $p=0.049$) on multivariable analysis. In the GBM subgroup, *CDK4* (OR 3.32 [95% CI, 1.04–9.97]; $p=0.042$) and *MSH6* alterations (OR 6.05 [95% CI, 1.12–33.1]; $p=0.037$) were associated with increased RN risk, whereas *MDM2* alterations remained associated with reduced risk (OR 0.07 [95% CI, 0.01–0.69]; $p=0.023$). In the *IDH*-mutant diffuse glioma subgroup (RN $n=9$; controls $n=201$), *ATRX* alterations were associated with lower RN risk (OR 0.10 [95% CI, 0.01–0.73]; $p=0.023$). *MGMT* status was not associated with RN risk. **Conclusions:** In this cohort, RN risk was not associated with demographic factors, tumor diagnosis, or MGMT status, but was associated with specific tumor genomic alterations. The enrichment of DNA damage response-related genes among those associated with RN suggests a potential biological link between tumor genomics and RN toxicity. Prospective validation will be required to determine the utility of these findings for genome-based risk stratification. Research Sponsor: None.

Direct oral anticoagulants versus low-molecular-weight heparin for venous thromboembolism in primary brain tumors: A TriNetX real-world analysis.

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Background: Venous thromboembolism (VTE) is a common complication in patients with primary brain tumors and is associated with poor outcomes. Although therapeutic anticoagulation is required for VTE treatment, its use in this population is challenging because of the increased risk of intracranial hemorrhage (ICH). Optimal anticoagulant selection remains uncertain, as concerns regarding ICH have limited randomized trial data in patients with primary brain tumors. Therefore, comparing ICH risk between direct oral anticoagulants (DOACs) and low-molecular-weight heparin (LMWH) is critical to optimizing anticoagulation in this high-risk group. **Methods:** This retrospective cohort study used the TriNetX Global Collaborative Network to identify adults (≥ 18 years) with primary malignant brain tumors who developed VTE within one year of tumor diagnosis. Patients with secondary malignant neoplasms were excluded. Cohorts included patients treated with DOACs (apixaban, rivaroxaban, edoxaban, or dabigatran) or LMWH (enoxaparin, dalteparin, or tinzaparin) after VTE diagnosis. The index date was defined by cohort entry criteria, and outcomes were assessed over 180 days. 1:1 propensity score matching was performed across demographic and clinical characteristics, including age, sex, race, cardiovascular disease, diabetes, kidney disease, coagulation disorders, obesity, and substance use. Intracranial hemorrhage and all-cause mortality were evaluated using risk estimates and Kaplan-Meier survival analyses. **Results:** After propensity score matching, 6,114 patients were included in each cohort. DOAC therapy was associated with a significantly lower risk of intracranial hemorrhage compared with LMWH over 180 days (3.9% vs 7.3%; risk ratio, 0.54; 95% CI, 0.46–0.64; $p < 0.001$). In addition, all-cause mortality at 180 days was significantly lower in the DOAC cohort than in the LMWH cohort (24.8% vs 31.3%; risk ratio, 0.79; 95% CI, 0.75–0.84; $p < 0.001$). These findings were consistent across the matched population, demonstrating improved safety and survival outcomes associated with DOAC use in patients with primary malignant brain tumors and VTE. **Conclusions:** In this large real-world cohort of adults with primary brain malignancy and VTE, DOAC treatment was associated with a lower intracranial hemorrhage risk and reduced mortality at 180 days compared with LMWH after propensity score matching. These findings support the safety of DOACs in patients with primary brain tumors and warrant further prospective evaluation of anticoagulant selection in this high-risk population. Research Sponsor: None.

Development of human B7H3/IL13Ra2 bispecific armored CAR-T for treatment of glioblastoma.

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Background: Glioblastoma (GBM) remains a highly lethal malignancy driven by infiltrative growth, molecular complexity, immune evasion, and therapeutic resistance. The limited efficacy of current treatments reflects antigen heterogeneity, an immunosuppressive tumor microenvironment, and restricted delivery across the blood–brain barrier with targeted therapy. Although earlier CAR-T therapies demonstrated preliminary activity in GBM, durable efficacy remains elusive. We have developed EPC-003, a fully human bispecific B7–H3/IL13R α 2 CAR-T engineered with a multi-mechanism armor to mitigate antigen heterogeneity, modulate the tumor microenvironment, and enhance persistence via central memory T-cell enrichment. **Methods:** Human anti-IL13R α 2, anti-B7–H3, and anti-PD–L1 scFvs were discovered from proprietary human B-cell libraries using mRNA display platform. A multi-mechanism armor was engineered by fusing the anti-PD–L1 scFv to a fine-tuned, immune cell-type specific IL-2 variant, identified through the unique cytokine engineering platform. These binding and functional modules were systematically optimized to generate EPC-003, a bispecific tandem CAR targeting IL13R α 2 and B7–H3 and incorporating a secreted multi-mechanism armor. CAR mechanisms, anti-tumor activity, and preclinical toxicity were evaluated. A proprietary clinical manufacturing process was established to produce a central memory T cell enriched CAR-T product. **Results:** The secreted armor of EPC-003 suppressed regulatory T-cell activation while selectively activating central memory T-cells, with the potential to enhance CAR-T cell persistence. In a 7-day G-Rex manufacturing process, EPC-003 demonstrated promising druggability with robust and reproducible CAR expression, and the proprietary cytokine cocktail consistently enriched the product to >65% central memory CAR-T cells. In orthotopic GBM models, intracranial administration of EPC-003 (0.4×10^6 and 1.2×10^6 CAR-T cells) induced tumor regression and showed dose-dependent anti-tumor activity. In preclinical toxicity studies, EPC-003 exhibited a favorable safety profile, with no body weight loss, cytokine release syndrome, or systemic clinical signs. No treatment-related pathological changes were observed across 25 examined organs. Immunohistochemistry revealed no evidence of brain hemorrhage in treated groups, with minimal monocyte infiltration in the pia mater observed only at the high dose. **Conclusions:** EPC-003, a multi-mechanism armored bispecific CAR-T, demonstrated favorable preclinical safety, developability, robust anti-tumor activity, and potential durability. These data support its advancement into an investigator-initiated clinical trial for the treatment of glioblastoma. Research Sponsor: None.

Which treatment is best? A systematic review and Bayesian network meta-analysis of adjuvant treatments for low-grade glioma.

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Background: The standard of care for low-grade glioma (LGG) includes resection with or without adjuvant treatment. It is currently unknown which adjuvant strategy is best. **Methods:** A systematic review of PubMed and EMBASE for randomized controlled trials (RCTs) evaluating adjuvant treatment for LGG published on or before 6/2/2025 was conducted as pre-registered (CRD420251072899). Study eligibility and data extraction were reviewed by two authors independently, and risk of bias was assessed via Cochrane RoB2. Two Bayesian network meta-analyses profiling *de novo* LGG were conducted with uninformative priors adjusting for baseline characteristics of each trial cohort. The pre-specified outcome measure was the distribution of posterior HR_{PFS} (primary meta-analysis) and HR_{OS} (secondary meta-analysis) for each identified treatment against observation. Posterior distributions were summarized with the posterior median hazard ratio (HR), and 95% equal-tailed credible interval (CrI). Further the probability of major benefit (HR≤0.6) and any magnitude harm (HR>1.0) were reported for each meta-analysis. **Results:** Six RCTs (all with low risk of bias) profiling 1,757 participants were identified for the primary meta-analysis (PFS). Seven RCTs (6 with low risk of bias 1 with high risk of bias) profiling 1,392 patients were identified for the secondary meta-analysis (OS). In total, six adjuvant treatment strategies were identified: radiotherapy (RT) + procarbazine/CCNU/vincristine (PCV), RT + temozolomide (TMZ), RT + CCNU alone, high-dose RT (HDRT, >54Gy), low-dose RT (LDRT; ≤54Gy), and TMZ. The posterior median HRs and 95% CrIs are reported in Table 1. For all profiled treatments, the probability of any benefit (HR<1.0) on the endpoint of PFS was >98% and >76% for OS. Additionally, the probability of major benefit (P1) and any magnitude harm (P2) were reported as clinically significant summary measures of all posterior distributions (Table 1). **Conclusions:** Based on the identified RCTs, RT+PCV was found to have the most favorable probability efficacy and RT+TMZ a similar distribution of treatment effect. RT+PCV and RT+TMZ had a >98% probability of any benefit for both endpoints. The probability of major benefit for RT+PCV and RT+TMZ was >99.9% and 84.8% for PFS and 71.3% and 63.3% for OS. Research Sponsor: NIH/NCI CCR Intramural Research Program.

Probability of benefit/harm of adjuvant therapy for low-grade glioma.						
	PFS	P1 _{PFS}	P2 _{PFS}	OS	P1 _{OS}	P2 _{OS}
PT+PCV	0.29 (0.19-0.43)	>99.9%	<0.1%	0.53 (0.32-0.84)	71.3%	0.4%
RT+TMZ	0.45 (0.27-0.76)	84.8%	0.2%	0.55 (0.33-0.91)	63.3%	1.1%
RT+CCNU	-	-	-	0.63 (0.28-1.42)	46.0%	13.4%
HDRT	0.59 (0.41-0.83)	55.0%	0.2%	0.86 (0.57-1.30)	4.4%	23.0%
LDRT	0.58 (0.44-0.76)	59.0%	<0.1%	0.89 (0.63-1.24)	1.4%	23.4%
TMZ	0.67 (0.47-0.97)	26.9%	1.4%	-	-	-
Observation	1 (Ref.)	-	-	1 (Ref.)	-	-

P1, probability HR≤0.6; P2, probability HR>1.0.

Characterization of contemporary practice patterns in the management of IDH-mutant glioma: A multidisciplinary multi-institutional survey.

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Background: The management of isocitrate dehydrogenase (IDH) mutant glioma is rapidly evolving following the recent FDA approval of the mutant IDH inhibitor, vorasidenib. Optimal treatment decisions for many specific clinical scenarios remain undefined leading different neuro-oncology providers to recommend different treatment approaches. The aim of this study was to characterize how clinicians collectively approach different clinical scenarios and evaluate how demographic and professional backgrounds influence decision-making in IDH-mutant glioma. **Methods:** An online survey was developed by a team of neuro-oncologists and radiation oncologists and distributed via email and X to clinicians treating patients IDH-mutant glioma. The survey included demographic questions and multiple case-based clinical scenarios with standardized response options. We compared the responses of neuro/medical oncologists, radiation oncologists, and neurosurgeons, and performed univariable regression to identify predictors of treatment preference, as well as to understand familiarity and enthusiasm with the use of IDH inhibitors. **Results:** A total of 153 clinicians (58% neuro/medical-oncologists, 34% radiation oncologists, 8% neurosurgeons) completed the online survey. Five of ten scenarios reached consensus (>75% agreement on a treatment option), while the remainder demonstrated heterogeneity of treatment approaches. Compared to neuro/medical oncologists, radiation oncologists were less likely than neuro/medical oncologists to recommend IDH inhibitor therapy (IRR 0.57, $p<0.001$) and more likely to recommend radiotherapy (IRR 1.54, $p<0.001$) or chemo-radiotherapy (IRR 1.47, $p<0.001$). Neuro-oncologists and neurosurgeons reported the most and least familiarity, respectively, with the use of IDH inhibitors whereas medical oncologists and radiation oncologists reported the most and least enthusiasm for IDH inhibitor use, respectively. **Conclusions:** Our survey results evidence substantial variation in real-world management of IDH-mutant glioma across specialties and institutions. While several clinical scenarios demonstrated strong therapeutic consensus, others revealed diverse approaches, underscoring the need for ongoing multidisciplinary collaboration and further advancement of evidence-based consensus to guide clinical decisions. Research Sponsor: None.

Rituximab pre-conditioning in a phase I study of CARv3-TEAM-E for recurrent glioblastoma (GBM): The INCIPIENT trial.

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Background: Chimeric Antigen Receptor (CAR) T cells for glioblastoma (GBM) have been limited by the challenge of targeting a single tumor antigen in a heterogeneous disease. To address this barrier, we generated a novel engineered T-cell product (CARv3-TEAM-E) that targets the EGFRvIII antigen while also secreting T-cell-Engaging Antibody Molecules (TEAMs) against wild-type EGFR. **Methods:** The INCIPIENT clinical trial is a first-in-human study of CARv3-TEAM-E in patients with GBM (NCT05660369). Patients with recurrent GBM were treated with intraventricular CARv3-TEAM-E T cells (10E6 cells per infusion) and one of three pre-treatment regimens: no lymphodepletion (N=3), lymphodepleting chemotherapy with cyclophosphamide and fludarabine (LDC) (N=7), or cyclophosphamide, fludarabine, and rituximab (LDC+R) (N=3). The primary objective was safety and tolerability. Immune cells were profiled in the cerebrospinal fluid (CSF) and peripheral blood by flow cytometry. **Results:** CAR T manufacturing was successful for all patients. There were no dose-limiting toxicities (DLT). Three patients were treated without LDC; all developed anti-CAR and/or anti-TEAM antibodies (i.e., anti-therapy antibodies) after a single infusion of CARv3-TEAM-E. Subsequently, 7 patients were treated with LDC prior to CARv3-TEAM-E, 5 of which underwent serial infusions (range 2-5 infusions). Four patients had reinfusions after which CAR T cells were not detected in the CSF. We therefore added rituximab to the LDC regimen. In the 3 individuals pre-treated with LDC+R, CAR T cells were detected in CSF not only after initial infusion (range 21-28 days) but also following repeat infusion in all patients (range 3-15 days post-reinfusion). Anti-therapy IgG was not detected in patients treated with LDC+R, as compared to 9/10 patients who developed an antibody response when rituximab was not administered. As of 12/15/2025, 10/13 patients are alive 6-30 months after first infusion, with 7 alive >14 months. **Conclusions:** Intraventricular CARv3-TEAM-E infusions were well-tolerated after LDC+R pre-conditioning and no DLTs were noted. The addition of Rituximab abrogated anti-therapy antibody formation and prolonged CAR T-cell persistence in 3/3 patients. Survival data reflect continued promise of CARv3-TEAM-E in patients with recurrent glioblastoma. Clinical trial information: NCT05660369. Research Sponsor: None.

Real-world outcomes from 3D-PREDICT glioma chemosensitivity testing of primary CNS tumors.

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Background: 3D-Predict Glioma is an *ex vivo* chemosensitivity assay that predicts response to 12 systemic agents using patient-derived 3D cell cultures. Prospective studies showed predictive accuracy, but real-world data linking assay-guided therapy selection to clinical outcomes remain limited. We analyzed outcomes at a tertiary cancer center. **Methods:** This retrospective-prospective chart review included patients with primary CNS tumors who underwent chemosensitivity testing at an urban cancer center since 3/2023. Demographics, tumor characteristics, assay results for the 12-drug panel, treatment selection, and clinical outcomes were abstracted. Drug response was categorized as response, moderate response, or no response. Survival analyses were performed using the Kaplan-Meier method. **Results:** Among the 96 patients, ECOG was 0 in 21 (22.1%), 1 in 37 (38.9%), 2 in 26 (27.4%), and 3 in 11 (11.6%). Insurance coverage included private (69, 71.9%), Medicaid/Medicare (14, 14.5%), Private plus Medicaid/Medicare (12, 12.5%), or self-pay (1, 1.0%). At the time of analysis, 85 patients (88.5%) were alive. Median age was 64 years (range 25–86; IQR 56–71), and 53 (55.2%) were female. Most were diagnosed with adult-type diffuse glioma (92, 95.8%), including 84 (87.5%) glioblastoma. Chemosensitivity testing failed in 10 (10.4%) cases due to insufficient tissue quantity or quality control. All remaining cases yielded 1 or more drugs with assay-predicted responses. Response rates for each drug are detailed in the Table. Mean time to results was 8.8 days (range 5–15). Assay-guided therapy was selected in 59.5%, predominantly temozolomide. The remaining patients received other agents on trial, standard-of-care physician's choice, no further therapy, or transferred care. Key endpoints analyzed included progression-free survival (PFS), PFS at 6 months, overall survival (OS), OS at 12 months, and time-to-progression (TTP) ratio. **Conclusions:** In a real-world CNS tumor cohort, 3D-Predict Glioma identified potentially active agents and influenced treatment selection in more than half of patients. Our series suggests that chemosensitivity-guided therapy is feasible in routine neuro-oncology practice. Research Sponsor: None.

Response rates by drug.

Drug	Newly Diagnosed	Progression	Pseudoprogression	All
Abemaciclib	17 (37.8)	10 (47.6)	2 (100.0)	29 (42.6)
Carboplatin	30 (60.0)	11 (50.0)	2 (100.0)	43 (58.1)
Dabrafenib	4 (8.0)	4 (17.4)	0 (0.0)	8 (10.7)
Etoposide	13 (25.5)	5 (21.7)	0 (0.0)	18 (23.7)
Everolimus	44 (100.0)	22 (100.0)	2 (100.0)	68 (100.0)
Irinotecan	23 (45.1)	9 (34.6)	0 (0.0)	32 (40.0)
Lomustine	2 (3.9)	1 (4.3)	0 (0.0)	3 (3.9)
Osimertinib	8 (17.4)	5 (23.8)	0 (0.0)	13 (18.8)
Procarbazine	50 (100.0)	23 (95.8)	2 (100.0)	75 (98.7)
Rucaparib	43 (86.0)	17 (73.9)	2 (100.0)	62 (82.7)
Temozolomide	20 (39.2)	10 (40.0)	2 (66.7)	32 (40.5)
Trametinib	20 (44.4)	6 (28.6)	0 (0.0)	26 (38.2)

Denominators defined by available results per drug; N (%).

Neoadjuvant treatment of recurrent high-grade gliomas with camrelizumab in combination with apatinib: A prospective phase II clinical study.

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Background: High-grade gliomas exhibit extremely recurrent and resistant to treatments, and require urgent therapeutic innovation. This phase II trial presents preliminary results of neoadjuvant camrelizumab (PD-1 inhibitor) combined with apatinib (VEGFR2 TKI) for recurrent high-grade gliomas. **Methods:** This single-center, single-arm, phase II trial (NCT04588987) enrolled patients (age >18, KPS $\geq$ 60) with recurrent high-grade gliomas suitable for re-resection after prior STUPP therapy. Patients received i.v. camrelizumab 200mg (D1) and oral apatinib 250mg (D1-D7). Surgery was performed 1 week post-drug discontinuation. Adjuvant treatment with i.v. camrelizumab 200 mg every two weeks (from 2 weeks $\pm$ 5 days post-surgery) in combination with continuous oral apatinib 250 mg/d (from 4 weeks post-surgery) was administered until death/unacceptable toxicity. Primary endpoint: overall survival (OS). Secondary endpoints: 1-year OS rate, 6-/12-month PFS rates, time to progression (TTP), KPS, and adverse events (AEs). **Results:** From October 2020 to December 2024, 28 patients were enrolled (median age 42 years [range 23-62]; 22 glioblastoma, 4 anaplastic astrocytoma, 1 anaplastic oligodendroglioma, 1 gliosarcoma). The 27 patients completed adjuvant therapy with follow-up, and 1 patients continue on adjuvant therapy. As of January 14, 2026, median OS for all patients was 11.100 months (95% CI: 8.818 -13.382), with 1-year OS rate 46.4%. Median PFS was 4.870 months (95% CI: 4.351 - 5.389), with 6-month PFS rate 39.3%. The 22 patients with recurrent glioblastoma (rGBM) showed the median OS of 11.670 months (95% CI: 8.303 -15.037), and the 1-year OS rate was 50.0%. The median PFS was 5.070 months (95% CI: 4.381 -5.759), with the 6-month PFS rate of 40.9% in the rGBM subgroup. Historical neoadjuvant anti-PD1 monotherapy for rGBM yielded OS 13.9 months and PFS 3.3 months (Nat Med. 2019). **Conclusions:** Camrelizumab in combination with apatinib neoadjuvant therapy showed excellent efficacy in recurrent high-grade gliomas, and was superior to PD1 inhibitor monotherapy neoadjuvant treatment in rGBM patients. Clinical trial information: NCT04588987. Research Sponsor: National Natural Science Foundation of China.

An alternative approach to limiting surgical and radiation stress in patients with glioblastoma.

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Background: While neuro-oncology has seen global advances in high-tech diagnostics and treatments for brain tumors, these innovations often overlook the principles of the body's adaptive response. Stress acts as a nonspecific driver of cancer progression and is intensified by aggressive therapies. An alternative approach involves harnessing general nonspecific adaptive reactions (GNARs), which are governed by the brain's regulatory systems. These anti-stress GNARs — specifically the reactions of training, calm activation, and elevated activation — form the foundation of "activation therapy" and are considered essential in the comprehensive management of high-grade gliomas (HGG). In glioblastoma, tumor growth exacerbates cerebral hypoxia, leads to endothelial damage, and promotes thrombosis and perifocal edema. During radiation therapy (RT), edema is further aggravated as a deleterious side effect of ionizing radiation on brain tissue. This study aimed to investigate whether adjunctive activation transcranial magnetic therapy (ATMT) can mitigate edema development and improve treatment outcomes. **Methods:** Data from 50 patients with HGG were analyzed. Using simple randomization, patients were divided into two groups: the Main group (n=25) received standard treatment plus two courses of ATMT during the early postoperative period and during RT; the Control group (n=25) received standard treatment without ATMT. Each ATMT session consisted of two exposures. The first exposure was performed in the morning on the hypothalamic projection area using a frequency algorithm of 0.3 Hz (5 min) – 3 Hz (1 min) – 9 Hz (1 min) with a daily exponential change in induction (B) from 3 to 1 mT (device: "Gradient-4M"). The second exposure was performed 2.5–3 hours later using pulsed ATMT on the perifocal zone of the removed tumor bed with the same frequency algorithm at B=15 mT (device: "Neuro-MSD"). **Results:** In the early postoperative period (prior to RT), ATMT reduced the frequency of acute stress development by 3.4-fold compared to controls. After the completion of RT combined with ATMT, stress inhibition was observed 1.6 times more frequently than in the control group. The induction of a stable "reaction of calm activation" via ATMT contributed to a decrease in perifocal edema volume by an average of 3.75-fold, compared to 1.04-fold in the control group (p=0.0180). Regression of neurological symptoms after RT was noted in 92% of patients who received two courses of ATMT versus 68% in the control group (p=0.0391). Furthermore, the absence of cognitive impairment after RT was observed in 80% of ATMT patients compared to 24% in the control group (p=0.0002). **Conclusions:** The adjunctive use of ATMT improves treatment outcomes in patients with HGG by developing and maintaining anti-stress reactions as an alternative to surgical and radiation-induced stress, thereby improving the patients' quality of life. Research Sponsor: None.

Management of first recurrence from IDH-wildtype glioblastoma with re-resection or stereotactic radiosurgery: A retrospective, international, multicenter study.

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Background: Optimal management of recurrent glioblastoma remains ill-defined. While re-resection is frequently provided as local salvage therapy, stereotactic radiosurgery (SRS) might represent a treatment approach for small, focal recurrences. We comparatively evaluated outcomes after re-resection and SRS for first recurrence of IDH-wildtype glioblastoma.

Methods: Adult patients with first radiographic recurrence of IDH-wildtype glioblastoma (WHO 2021 classification) were identified. Information on patients managed with re-resection were collected through the international eight-center database of the RANO resect group, and patients managed with SRS were collected by twelve centers from the IRRF study group. Survival after recurrence was analyzed using Kaplan–Meier estimates and Cox proportional hazards models. Inverse probability of treatment weighting (IPTW) was applied to mitigate baseline imbalances. **Results:** Overall, 567 patients were included (re-resection: $n = 310$; SRS: $n = 257$). Compared with SRS, patients managed with re-resection were younger and had larger contrast-enhancing recurrence volumes. Despite those baseline differences, overall survival did not differ between treatment modalities (10.2 [95%CI 9.3–11.7] vs. 11.1 [10.3–12.8] months; HR 1.12, 95%CI 0.93–1.35; $p = 0.231$). Also, no survival differences between treatment groups were observed when effects of potential baseline confounders including tumor volume were minimized using IPTW. Notably, among patients typically not considered SRS candidates due to tumor volumes $>10 \text{ cm}^3$ ($n = 234$), maximal re-resection of the enhancing tumor (RANO class 1–2) was associated with survival comparable to SRS-treated low-volume tumors $\leq 10 \text{ cm}^3$ (9.1 [7.7–11.5] vs. 11.0 [9.9–12.8] months; HR 1.27, 0.95–1.69; $p = 0.106$) whereas incomplete re-resection (RANO class 3) was associated with less favourable survival. In the subgroup of patients with focal recurrences in whom local physicians from the IRRF consortium perceived clinical equipoise between treatment modalities but eventually performed SRS ($n = 112$), IPTW-adjusted analyses demonstrated no significant difference in overall survival compared with re-resected patients (HR 0.90, 0.65–1.25; $p = 0.539$). **Conclusions:** While complete re-resection is prognostic in recurrent glioblastoma, SRS might represent a reasonable therapeutic approach for selected individuals with small low volume tumor recurrence. Given substantial baseline differences between patients treated with re-resection and SRS and potential treatment provider bias, prospective trials are warranted to guide nuanced decision-making. Research Sponsor: None.

Phase II trial evaluating nivolumab in patients with recurrent IDH-mutant gliomas with and without hypermutation phenotype.

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Background: Tumor mutational burden (TMB) is an emerging biomarker for the prediction of immune therapy success in solid tumors. Response to immune checkpoint inhibitor (ICI) treatment in rare gliomas with biallelic mismatch repair deficiencies has been attributed to their hypermutation phenotype (HMP). This has not been tested in other gliomas. We developed a phase II clinical trial using nivolumab in recurrent IDH-mutant gliomas evaluating response in tumors with HMP (approximately 10% of cases) and in tumors with non-HMP (NHMP). Here we report the results of the analysis of the NHMP cohort. **Methods:** Adults with recurrent IDH-mutant glioma, KPS $\geq$ 60, normal organ function, with known somatic TMB (analyzed at NIH) were enrolled in a phase II trial. Nivolumab was given at 480mg IV every 28-day cycle with a maximum of 16 cycles. The primary endpoint is PFS rate at 6 months (PFS6) in both HMP and NHMP cohorts. Responses to treatment were evaluated by MRI every 2 cycles using iRANO criteria. Simon's two-stage design was used to independently evaluate the HMP/NHMP cohort. For the NHMP cohort, the null and alternative hypotheses for PFS6 are 0.2 and 0.4, respectively. A total of 30 were planned to be accrued across stages I and II. If $\geq$ 10 patients are progression-free at 6 months, the null hypothesis will be rejected, indicating that the treatment is promising for patients with NHMP IDH-mutant gliomas. The design controls the type I error at 0.05 and yields a power of 0.8. Tumor samples and peripheral blood were collected for correlative studies. Patient-reported outcomes (PRO) were evaluated by longitudinal symptom burden analysis using Brain Tumor Module of the MD Anderson Symptom Inventory. **Results:** As of January 2026, thirty patients were enrolled and treated on the NHMP cohort (TMB $\leq$ 5 mut/Mb). Among 30 evaluable patients, 20 were male, median age 44 and KPS 90. Histological diagnosis included 22 astrocytoma (grade 3, n=10; grade 4, n=12) and 8 oligodendroglioma (grade 2, n=1; grade 3, n=7). Median number of prior recurrences is 2, ranging from 1 to 5. At the time of analysis, all 30 evaluable patients were off study treatment: 7 completed all 16 cycles, 17 had disease progression, 3 withdrew to start other management. Three patients were off treatment due to treatment related grade 3 colitis, pneumonitis and dry mouth. Eleven and 8 out of 30 patients were progression free at 6 and 12 months, respectively. PRO and correlative studies are ongoing. **Conclusions:** Nivolumab is well tolerated and has shown efficacy in a cohort of patients with recurrent IDH-mutant gliomas with low TMB. Clinical benefit measured by objective response, PFS, OS and PRO, along with longitudinal immune monitoring, will help determine whether tumor TMB correlates with immunologic and clinical response to ICI therapy in IDH-mutant gliomas. Clinical trial information: NCT03718767. Research Sponsor: NIH Intramural Research.

A phase 2 double-blind, randomized, prospective, placebo-controlled study of NanO₂ combined with radiation and temozolomide in patients with newly diagnosed glioblastoma: RESTORE.

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Background: Glioblastoma (GBM) contains extensive hypoxic regions due to tumor-associated thrombosis and abnormal vasculature. Hypoxia drives resistance to radiation (RT) and temozolomide (TMZ) by limiting oxygen-dependent DNA damage, enabling DNA repair, and reducing drug efficacy and delivery. The RESTORE trial (NCT03862430) is the first randomized, prospective, placebo-controlled study of NanO₂ (2% w/v dodecafluoropentane emulsion) in GBM, a fluorocarbon-based oxygen therapeutic hypothesized to reoxygenate hypoxic GBM tissue, with the goal of enhancing the efficacy of chemoradiation. **Methods:** Patients with newly diagnosed GBM (WHO 2021) received standard-of-care radiation (60 Gy) with concurrent TMZ (75 mg/m²/day). Patients were randomized 2:1 to receive either NanO₂ or 0.9% sodium chloride administered intravenously immediately prior to each RT fraction, with continuous supplemental oxygen given during the infusion and RT. Following chemoradiation, patients completed a four-week recovery period before initiating adjuvant TMZ for 6 cycles. The primary endpoint is progression free survival and secondary endpoints include overall survival, objective response rate, pseudoprogression rate, and patient reported outcomes. **Results:** Between May 2023 and October 2025, 93 patients were treated (safety set). The study has completed the planned enrollment. Median age was 63 years (range, 19–84) and 57% were men. As of the data cutoff on 12/29/25, all patients completed the follow up visit 4 weeks after chemoradiation. Sixty-eight patients (73%) remained on study undergoing adjuvant TMZ or in long-term follow-up. Twenty-one patients passed of tumor progression and 4 patients withdrew consent. The median duration on study was 8.7 months (range, 1.3–31.4). During chemoradiation and the four-week recovery, 63 treatment-emergent adverse events (TEAEs) of CTCAE severity grade ≥3 were reported in 37% of patients, with brain edema, lymphocyte count decreased, and platelet count decreased being the most frequently reported. Twenty-six treatment-emergent serious adverse events (TESAEs) occurred in 19% of patients, with embolism, pulmonary embolism, and seizure being the most frequently reported. Three TESAEs were assessed as possibly or probably related to study drug; none were unexpected. Survival follow up is ongoing. **Conclusions:** In this blinded, pooled safety analysis of a randomized phase 2 trial in newly diagnosed GBM, the study treatment was well tolerated and no new safety signals were identified. Treatment allocation remains blinded. Efficacy outcomes and arm-specific safety analyses will be reported after completion of the primary endpoint analysis. Clinical trial information: NCT03862430. Research Sponsor: NuvOx Therapeutics.

Mapping the exhausted and tolerized myeloid populations in the glioblastoma tumor microenvironment.

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Background: Glioblastoma (GBM) is a highly malignant brain tumor characterized by an immunosuppressive microenvironment and rapid development of therapeutic resistance. In GBM, myeloid cells can comprise 30–50% of the tumor and critically regulate its immune microenvironment. Evidence from aging and CNS diseases suggests that microglia can adopt dysfunctional states of exhaustion and tolerance that extend beyond the M1/M2 paradigm, thus prompting us to investigate whether these phenotypes contribute to immune escape and progression of GBM. **Methods:** Paired RNA-seq of tumor specimens from newly diagnosed and recurrent GBM patients (n=14) was used to examine aging-related gene expression during treatment and progression. Open-access human glioma single-cell RNA-seq data (GSE182109) were analyzed to characterize exhaustion and tolerance across macrophage subpopulations based on molecular/metabolic signatures. **Results:** Patient tumor RNA-Seq revealed that the aging-related TREM2-APOE axis is present in recurrent GBM, suggesting accelerated brain aging. Single-cell RNA-seq identified nine myeloid clusters, including four microglial states (homeostatic-, activated-, AP-, and a-microglia) and two macrophage populations (anti-inflammatory and immunosuppressive). We found that AP-microglia showed disease-associated activation, with high CD45/CD11C/TREM2 expression and concurrent upregulation of the exhaustion markers PD-L1 and CD38. Moreover, microglial activation-related signaling in AP-microglia includes increased STAT1/2-IRF9 signaling, which can promote immunosuppression by inducing PD-L1. On the other hand, a-microglia is unique in its high expression of activation-restraining and tolerance markers, such as SPRY/P2RY13, rather than the classic microglial marker TMEM119/P2RY12. Both AP-microglia and a-microglia are shown to lose expression of the inflammatory cytokines TNF- α and IL-1 β , consistent with the characteristics of exhausted and tolerized microglia. Unlike resident microglia, the immunosuppressive macrophage cluster exhibits a monocyte-tolerized phenotype, with downregulated FABP4 and increased SOD2, CLEC4E, and SLC2A6. It also shows a similar panel of LPS-induced monocyte exhaustion with TLR4/MyD88/SRC and STAT3/IL-10 upregulation. **Conclusions:** Our analysis indicates that AP-microglia are exhausted and a-microglia are tolerized in GBM, with shared markers of dysfunction across macrophages linking myeloid impairment to immune suppression and treatment-associated brain aging. These findings implicate myeloid exhaustion in GBM immune escape and identify potential therapeutic targets. Research Sponsor: Louise McMichael Miracle Fund.

A 3D tumorwide multi-omic atlas of intratumoral heterogeneity in *IDH*-mutant glioma.

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Background: Isocitrate dehydrogenase mutant (IDHmut) glioma affects over 20,000 adults per year. Treatment failure often results from intratumoral heterogeneity, in which genomic subclones undergo selection for treatment-resistant populations. Understanding this heterogeneity is critical to selecting therapeutic combinations that are efficacious across the entire tumor, but few genomic studies go beyond analyzing a single tumor sample per patient. **Methods:** 3D whole tumor sampling was used to obtain 324 spatially mapped samples from 32 IDHmut gliomas. Whole exome (n=323), RNA (318), ATAC sequencing (92), and Hi-C (14) were performed. PyClone reconstructed clonal evolution, weighted gene/peak correlation network analyses derived co-expression (RNA) and gene regulatory (ATAC) programs, and comparison of tumor Hi-C results to normal brain identified tumor-specific chromatin loops. **Results:** Regional tumor content (purity) inversely correlated with distance from tumor centroid ($R = -0.32$, $p = 2.8 \times 10^{-8}$) and inter-sample distance was associated with subclonal ($R = 0.24$, $p = 8.1 \times 10^{-15}$) and transcriptional ($R = 0.12$, $p = 1.0 \times 10^{-5}$) similarity. Beyond IDH1 in the combined 17 astrocytomas and 15 oligodendrogliomas, tumor-wide alterations were recurrently observed in TP53 (altered in 64%; tumor-wide in 58%), ATRX (55%; 39%), TERT promoter (45%; 45%) and FUBP1 (18%; 6%). Despite high cohort prevalence, glioma-associated drivers CIC (altered in 42%), PIK3CA (36%), and ARID1A (18%) were tumor-wide in only one patient each, while MUC4 (33%), NOTCH1 (27%), SETD2 (24%), and PIK3R1 (15%) were never observed in the tumor founding clone. Tumors with CIC alterations harbored a median of 5 unique mutations with a median combined tumor-wide cancer cell fraction of 45%. Hi-C identified 5,579 tumor-specific promoter-enhancer interactions across 4,144 loops. The genes associated with these promoters enriched for tumor-specific RNA programs associated with OPC signature ($p_{\text{adj}} = 3 \times 10^{-14}$), NPC signature ($p_{\text{adj}} = 3.87 \times 10^{-14}$), and neuronal mimicry (1.2×10^{-13}). We discovered adversely prognostic gene expression programs in astrocytoma independently validated in chromatin regulatory programs. **Conclusions:** Tumor-wide sampling of IDHmut glioma revealed evidence of radial tumor growth and 3D patterns of cellular organization, in sharp contrast to intermixed patterns in IDH wildtype glioma. Most inter-patient heterogeneity in driver alterations was subclonal. Our data also revealed regulatory loops that explain tumor cell-specific expression signatures. A significant, adverse prognostic marker in astrocytoma was discovered and cross-validated. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

Identification of prognostically relevant residual tumor burden in glioblastoma after surgery: A comparative analysis of MR-based RANO resect classes vs [¹⁸F]FET PET.

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Background: Accurate assessment of postoperative residual tumor burden is critical in *IDH*-wildtype glioblastoma. The MRI-based RANO resect classification stratifies patients according to postoperative contrast-enhancing and non-contrast enhancing tumor volume but may underestimate metabolically active residual disease. The additional prognostic value of postoperative [¹⁸F]FET PET beyond MRI is yet unclear. **Methods:** This retrospective bicentric study included 140 patients with newly diagnosed *IDH*-wildtype glioblastoma and evaluable postoperative MRI and [¹⁸F]FET PET. Residual tumor volumes were segmented on MRI and classified according to the RANO resect system. PET-derived residual metabolic tumor volumes were defined using PET RANO 1.0 criteria. Spatial agreement between MRI- and PET-based volumes was quantified using Dice coefficients. Associations with overall survival were analyzed using Cox regression. Incremental prognostic value of PET was assessed using an imaging-only model (contrast-enhanced T1 (T1CE) vs. T1CE + PET) and a fully adjusted model including clinical covariates. **Results:** PET-derived residual tumor volumes exceeded MRI-defined volumes and showed low spatial concordance with MRI (Dice coefficient: 0.01–0.25) across all RANO resect classes. Postoperative PET-, T1CE-, and T2/FLAIR-derived tumor volumes were each associated with overall survival. Increasing PET-derived residual tumor burden was associated with a continuous increase in mortality risk. In multivariable Cox regression, PET-derived residual tumor volume remained independently associated with overall survival (adjusted hazard ratio 1.021 per cm³, 95% CI 1.008–1.033; ***p* = 0.0024). In the imaging-only model, addition of PET improved time-dependent discrimination between 6 and 24 months (Δ AUC(t) 0.03–0.07) and increased Harrell's C (Δ C $\approx$ 0.03). In the fully adjusted model, PET provided significant non-redundant prognostic information (likelihood ratio test, **p* = 0.0049). **Conclusions:** Postoperative [¹⁸F]FET PET identifies metabolically active residual tumor not adequately captured by MRI and provides additional prognostic information beyond MRI-based assessment. Integration of PET into postoperative evaluation may refine prognostic stratification in *IDH*-wildtype glioblastoma. Research Sponsor: None.

Phase I/II study of liposomal curcumin in combination with standard radiation and temozolomide in patients with newly diagnosed high-grade gliomas.

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Background: Liposomal curcumin (LC) is an intravenous formulation designed to enhance curcumin delivery and modulate inflammatory, oxidative, and oncogenic pathways relevant to high-grade glioma (HGG), including dysregulated kynurenine metabolism. Preclinical studies demonstrate synergy between LC and chemoradiation. This Phase I/II study was designed to determine the recommended Phase II dose (RP2D) of weekly IV LC with radiotherapy and temozolomide (RT/TMZ) in newly diagnosed HGG (primary objective), assess safety and feasibility (secondary objective), and preliminary efficacy (exploratory objective). **Methods:** This open-label, sequential dose-escalation study used the TITE-BOIN Bayesian design to evaluate LC at 300, 350, and 400 mg/m². Patients received standard chemoradiation (2 Gy × 5 days/week × 6 weeks with concomitant TMZ 75 mg/m²/day), followed by standard adjuvant TMZ and weekly LC infusions over 3 hours for a target of 34 doses, with optional continuation. Eligible patients had newly diagnosed HGG (WHO grade 3 or 4) and KPS ≥70%. Patients were evaluable if they received ≥80% of planned LC infusions and ≥60% of planned TMZ dosing during the 10-week toxicity evaluation period. Radiographic response was assessed per RANO 2.0. **Results:** Twenty-five patients were treated: 300 mg/m² (n=6), 350 mg/m² (n=12), and 400 mg/m² (n=7); all patients assigned to 400 mg/m² were treated at 350 mg/m² per Safety Review Committee recommendation. All patients had glioblastoma or molecular glioblastoma, IDH-wildtype, WHO grade 4 per 2021 WHO classification (MGMT promoter methylation status: 7 methylated, 1 indeterminate, 17 unmethylated). Median age was 56 years (range, 43–75); median KPS was 90 (range, 70–100). Two protocol-defined dose-limiting toxicities occurred at 400 mg/m²: grade 4 pancytopenia and grade 1 hemolysis. LC-related grade ≥3 toxicities occurred in 4 patients (16%) and included confusion, seizure, thromboembolic event, cerebral edema, lymphopenia, thrombocytopenia, fatigue (all grade 3), and pancytopenia (grade 4). There were no LC-related deaths. Based on the TITE-BOIN design and cumulative safety data, 350 mg/m² was identified as the RP2D. With a median follow-up of 12.9 months (range, 2.4–27.3 months) as of 1/23/2026, median progression-free and overall survival have not been reached. At 6 and 12 months from first LC infusion, 95% and 87% of uncensored patients (n=18, n=13), respectively, remained alive. **Conclusions:** LC combined with standard chemoradiation was safe and well tolerated, with encouraging exploratory signals of disease control in newly diagnosed glioblastoma. Further evaluation in an expanded Phase II/III study is planned. Clinical trial information: NCT05768919. Research Sponsor: Signpath Pharma.

Phase I trial to evaluate the safety and tolerability of fb-PMT in patients with recurrent glioblastoma.

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Background: Proliferative, pro-angiogenesis, and pro-inflammatory actions mediated by L-thyroxine in glioblastoma (GBM) are initiated at cell surface thyrointegrin $\alpha v \beta 3$ receptors for thyroid hormone, located on the extracellular domain of $\alpha v \beta 3$ integrin. Thyrointegrin $\alpha v \beta 3$ receptors are over-expressed in cancer and rapidly dividing endothelial cells. fb-PMT (NP751) is a macromolecule in which fluorobenzyl is conjugated to monodisperse polyethylene glycol via mono-triazole tetraiodo thyroacetic acid, with high affinity and specificity for thyrointegrin $\alpha v \beta 3$ receptors. In pre-clinical murine xenograft models, fb-PMT resulted in a dose-dependent suppression of GBM tumor growth and viability, and histopathological analysis revealed loss of the vascularity along with extensive tumor necrosis and apoptosis. Genomic micro-array studies suggested multiple growth pathways in GBM are modulated by fb-PMT. Based on this promising pre-clinical data, we conducted a first-in-human Phase 1 study of fb-PMT in patients with recurrent GBM. **Methods:** Patients with first or second recurrence of GBM were enrolled to receive fb-PMT via subcutaneous injection once daily for 28-day cycles, following a 3+3 design. Predefined dose levels were 0.08, 0.24, 0.48, 0.96, and 1.44 mg/kg/day, respectively. The study objectives were to evaluate the safety and tolerability of daily administration of fb-PMT, and establish the recommended phase 2 dose (RP2D) of fb-PMT. Exploratory objectives included pharmacokinetic profiling of fb-PMT, expression of $\alpha v \beta 3$ integrin, fb-PMT, and other proteins in available tumor samples, and estimating preliminary efficacy of fb-PMT. **Results:** As of January 2026, accrual has been completed, with 22 patients enrolled and 20 patients completing at least one treatment cycle. Treatment with fb-PMT was well tolerated across the 5 dose levels examined. No serious adverse events (SAEs) related to fb-PMT and no dose-limiting toxicities occurred; the RP2D is 0.96 mg/kg/day. PK analysis demonstrated a dose-dependent increase in systemic drug exposure with escalating doses. Immunohistochemical evaluation of integrin $\alpha v \beta 3$ expression in available tumor samples detected target expression, with variable levels of integrin $\alpha v \beta 3$ expression and predominant localization to tumor-associated vasculature and regions of necrosis and hemorrhage. Preliminary efficacy evaluation is ongoing, with two patients in Cohort 4 (0.96 mg/kg/day) having partial response and remaining on study (cycle 35+ and cycle 26+, respectively). **Conclusions:** This Phase 1 study demonstrated that treatment of recurrent glioblastoma with fb-PMT was safe and well tolerated, with a predictable pharmacokinetic profile. Two patients remain on therapy beyond 24 months. Future studies are planned. Clinical trial information: NCT05226494. Research Sponsor: NanoPharmaceuticals LLC.

Suicide gene therapy for recurrent glioblastoma using allogeneic bone marrow-derived mesenchymal stem cell gene delivery (MSC/CD): A first-in-human, dose-escalation phase I clinical trial.

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Background: Glioblastoma (GBM) remains an incurable brain tumor characterized by complex heterogeneity and poor prognosis, even with maximal multimodal therapy. Innovative treatments for recurrent GBM are urgently needed to complement existing therapies. This study explores the feasibility, safety, and efficacy of a novel suicide gene therapy using allogeneic mesenchymal stem cells (MSCs) expressing cytosine deaminase (CD) in combination with 5-fluorocytosine (5-FC). **Methods:** A Phase 1, single-center, non-randomized, dose-escalating study was conducted to evaluate the safety and efficacy of mesenchymal stem cell expressing cytosine deaminase (MSC/CD) therapy in 10 patients with recurrent GBM. Patients received intratumoral injections of MSC/CD followed by oral 5-FC. Pharmacokinetic profiling, pharmacodynamic analysis, targeted panel sequencing, whole transcriptome analysis, integrative omics analysis, and multiplexed immunofluorescence imaging were performed to assess drug conversion and identify predictable candidate biomarkers. Safety and survival outcome were monitored by evaluating adverse events (AEs) and clinical data. **Results:** MSC/CD therapy was well-tolerated, with most AEs being mild to moderate. There was no drug toxicity related with dose escalation. Severe AEs ($\geq$ Grade 3) were rare and unrelated to the study drug. Effective conversion of 5-FC to 5-fluorouracil (5-FU) was observed in the brain, with detectable levels in the cerebrospinal fluid, confirming the feasibility of intracranial drug delivery. The median progression-free survival was 5.4 months, and the overall survival was 16.3 months. RNA transcriptomic analysis revealed two molecular subclusters with distinct biological characteristics, correlating with different progression-free survival outcomes. The integrative omics analysis revealed that specific cell cycle-related genes were found to be highly expressed in the non-responder group of patients, suggesting that elevated levels of these genes may be associated with resistance to treatment. **Conclusions:** This study demonstrates that MSC/CD therapy is a feasible, safe, and potentially effective treatment for recurrent GBM. The identification of distinct molecular subtypes and candidate genes offers a potential biomarker for patient selection and therapeutic targeting. Further studies are warranted to validate these findings and optimize therapeutic strategies. Clinical trial information: NCT04657315. Research Sponsor: the Ministry of Trade, Industry & Energy (MOTIE, Korea); 10067378.

Intrathecal iPSC-derived natural killer cells combined with the Stupp regimen for newly diagnosed WHO grade 4 glioma: A phase I trial.

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Background: WHO grade 4 glioma has a poor prognosis despite standard Stupp therapy. Induced pluripotent stem cell-derived allogeneic natural killer cells (iPSC-NK) represent a standardized and scalable cellular immunotherapy with consistent cytotoxic potential. This Phase I study evaluated intrathecal iPSC-NK cells combined with the Stupp regimen in newly diagnosed WHO grade 4 glioma. **Methods:** Thirteen newly diagnosed WHO grade 4 glioma patients (median age 46 years; IDH-wildtype n=11; MGMT-methylated n=6) received standard chemoradiotherapy followed by intrathecal iPSC-NK cell infusions. iPSC-NK cells were administered at escalating doses (2×10^7 , 6×10^7 , 2×10^8 cells/cycle) via lumbar puncture (n=8) or Ommaya reservoir (n=5) over four 28-day cycles, with temozolomide priming 5 days before each infusion. The primary endpoint was safety (serious adverse events, $\geq$ Grade 3 toxicities); secondary endpoints included progression-free survival and pharmacokinetic/pharmacodynamic immune analyses. **Results:** Across 54 intrathecal iPSC-NK infusions, treatment-related toxicities were predominantly low grade: fever occurred as Grade 1 in 35 (64.8%) and Grade 2 in 9 (16.7%) infusions; headache as Grade 1-2 in 19 (35.2%) and Grade 3 in 1 (1.9%) infusion; and cytokine release syndrome was limited to Grade 1 events (44/54, 81.5%), with no $\geq$ Grade 2 CRS or ICANS. Median PFS was 17.41 months, while median OS was not reached at a median follow-up of 22.47 months (data cutoff: January 18, 2026). PK analysis showed detectable iNK cells in CSF on Days 1-3 post-infusion, peaking on Days 1-2 and declining by Day 3. PD analyses demonstrated rapid activation of CD4⁺/CD8⁺ T cells (CD69⁺) and expansion of myeloid populations. Olink proteomics revealed consistent upregulation of cytotoxic (GZMA/B), chemokine (CXCL/CCL), and inflammatory cytokines (TNF, IFN- γ). **Conclusions:** iPSC-NK cells combined with the Stupp regimen demonstrated a favorable safety profile, induced early immune activation within the central nervous system, and showed encouraging preliminary efficacy in patients with WHO grade4 glioma. Clinical trial information: NCT06147505. Research Sponsor: National Natural Science Foundation of China; 82472981; XellSmart Bio-pharmaceutical (Suzhou) Co., Ltd.

Comparative response assessment using PET-RANO 1.0 and RANO 2.0 in vorasidenib-treated *IDH*-mutant gliomas: The VORAFET study.

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Background: MRI-based response assessment may be suboptimal for capturing early treatment effects during isocitrate dehydrogenase (*IDH*) inhibition. We compared metabolic and morphological response classification using PET-RANO 1.0 and RANO 2.0 in vorasidenib-treated *IDH*-mutant gliomas and assessed treatment-related metabolic changes. **Methods:** All consecutive patients treated at Veneto Institute of Oncology and Padua University Hospital with vorasidenib (VOR) under a compassionate-use program (June 2024–March 2025) with baseline and follow-up [¹⁸F]FET PET/MR were retrospectively included. Response was assessed every 3 treatment cycles according to PET-RANO 1.0 and RANO 2.0. PET-positive tumor volumes and tumor-to-background ratios (TBR_{max} , TBR_{mean}) were analyzed. MRI response was evaluated using volumetric RANO 2.0 criteria. The VORAFET study was approved by the local Ethics Committee. **Results:** Twenty-six patients were included (10 astrocytomas, 16 oligodendrogliomas; 22 WHO grade 2, 4 non-enhancing WHO grade 3). Median follow-up from VOR initiation was 9 months (IQR 9–11). According to PET-RANO 1.0, partial metabolic responses (PET-PR) increased over time, from 20% at 3 months to 30.8% at 6 months and 63.6% at 9 months, while metabolic progression (PET-PD) was already detected in 18.2% at 9 months. In contrast, RANO 2.0 identified no partial responses at any timepoint, classifying most patients as stable disease (84.2%) or minor response (10.5%), with progression detected in only 5.3% at 9 months. Quantitative PET analysis showed an early and sustained reduction in metabolic activity. TBR_{mean} decreased significantly at 3 months (mean difference [MD] -0.04 ; 95% CI -0.08 to -0.01) and continued to decline at 9 months (MD -0.07 ; 95% CI -0.11 to -0.02). Compared to baseline, at 9 months, TBR_{max} decreased from 2.7 to 2.0 (MD -0.5 ; 95% CI -0.8 to -0.2) in all patients included. No significant changes were observed in PET volumes. Similarly, FLAIR-based tumor volume showed no significant variation (at 9 months: MD -2.2 ; 95% CI -5.1 to 0.7). **Conclusions:** PET-RANO 1.0 enabled earlier detection of treatment response and progression compared with MRI-based RANO 2.0, highlighting clinically relevant limitations of morphology-driven MRI-based assessment. These findings support the clinical integration of amino acid PET into response monitoring strategies and warrant prospective validation of PET-derived biomarkers in *IDH*-mutant gliomas. Research Sponsor: None.

Phase II clinical study of ACT001 combined with radiotherapy in newly diagnosed pediatric diffuse intrinsic pontine glioma.

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Background: Diffuse intrinsic pontine glioma (DIPG) is an extremely lethal type of malignant tumor in the central nervous system of children. Currently, standard radiotherapy has limited efficacy, and there is an urgent need to explore novel therapeutic regimens. This study aims to evaluate the safety and efficacy of ACT001, a novel blood-brain barrier-permeable agent, combined with standard radiotherapy in the treatment of newly diagnosed pediatric DIPG.

Methods: This open-label, single-arm, multicenter phase II trial enrolled 5–15-year-old patients with newly diagnosed DIPG. Patients received radiotherapy (54 Gy/30 fractions) plus ACT001 (700 mg/m² BID orally, fasting) for 6 weeks (concurrent phase), followed by ACT001 maintenance until progression/toxicity. The primary endpoints were objective response rate (ORR) and overall survival (OS), while the secondary endpoints included progression-free survival (PFS), 1-year OS rate, and safety. Statistical analyses used Kaplan-Meier and Cox regression. **Results:** A total of 41 patients were screened, with 33 included in the full analysis set (FAS). Thirty-one patients completed the concurrent phase and were included in the per-protocol (PP) set. The median age was 8 years; 18.2% (6 cases) were biopsy-confirmed (83.3% harboring the H3K27M mutation) and 81.8% (27 cases) were radiologically diagnosed. In the FAS, ORR was 30.3% (10 partial responses [PR]), and the disease control rate was 75.8%; 21.2% (7 cases) in the PP set achieved >50% tumor reduction in pontine lesions. Median OS was 12.7 months (95% CI: 8.7–NA) with a 1-year OS rate of 50.1%; median PFS was 5.9 months (95% CI: 4.3–7.8) with a 6-month PFS rate of 45.3%. Multivariate analysis showed a higher baseline Lansky score was a favorable prognostic factor for OS (HR=0.899, P=0.0069), and achieving PR was favorable for PFS (HR=0.232, P=0.0162). Nineteen patients received salvage therapy post-progression; those undergoing re-irradiation had a median OS of 17.9 months, significantly better than non-re-irradiated patients (P=0.031). Ninety-six point nine percent (32/33) of patients experienced treatment-related AEs (mostly grade 1–2). The incidence of grade ≥3 AEs was 18.2%, with the most common being lymphopenia, weight loss, and upper respiratory tract infection (each 6%). No treatment-related deaths occurred, and no patients discontinued ACT001 due to toxicity. Additionally, 96.9% (31/32) of patients had improved or stable Lansky scores post-treatment. **Conclusions:** ACT001 combined with standard radiotherapy exhibits certain antitumor activity in the treatment of newly diagnosed pediatric DIPG, with improved OS compared to historical data, as well as a manageable safety profile and good tolerability. This regimen provides a new treatment option for pediatric DIPG and warrants further verification in larger-scale randomized controlled trials. Clinical trial information: ChiCTR2300074598. Research Sponsor: None.

Application of PET RANO 1.0 criteria and associations with outcome in *IDH*-mutant gliomas: A retrospective cohort study.

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Background: Amino acid PET is increasingly used to guide clinical decisions in glioma. For standardized response assessment, PET RANO 1.0 criteria have been formulated, but are primarily consensus-based and lack validation in molecular subgroups of diffuse gliomas. **Methods:** In this retrospective cohort study, patients with newly diagnosed or recurrent *IDH*-mutant glioma and at least two O-(2-[¹⁸F]-fluoroethyl)-L-tyrosine ([¹⁸F]FET) PET scans in 02/2013 - 08/2025 were included. PET was evaluated using PET RANO 1.0 criteria based on maximum and mean tumor-to-background ratios (TBR_{max}/TBR_{mean}) and PET volume. Intervention-free survival (IFS) was used as endpoint. **Results:** Overall, 219 patients (110 [50.2%] oligodendroglioma, 106 [48.4%] astrocytoma, 3 with unknown 1p/19q status; 115 [52.5%] CNS WHO 2, 80 [36.5%] CNS WHO 3, 23 [10.5%] CNS WHO 4, 1 grading inconclusive) with 251 lesions were included. Median age at first PET was 45 years (range: 21-75), and 117 (53.4%) patients were male. In total, 220 treatment lines (173 [78.6%] first line treatment; 47 [21.4%] recurrence/progression) were followed, of which 135 (61.4%) involved radiotherapy and/or systemic treatment, and 85 (38.6%) observation. Median time between PET scans was 6.7 months (2.4-11.8). In first-line treatment at baseline, PET-based measurable disease was seen in 126/173 (72.8%), non-measurable in 38/173 (22.0%) and no measurable disease in 9/173 (5.2%). PET-based complete remission (PET-CR) was observed in 7/173 (4.0%), partial remission (PET-PR) in 32/173 (18.5%), stable disease (PET-SD) in 74/173 (42.8%), and progressive disease (PET-PD) in 60/173 (34.7%) patients. The primary driver of PET-PD was an increase in PET volume alone (27/60, 45.0%) or in combination with an increase in TBR_{max}/TBR_{mean} (19/60, 31.7%), followed by new measurable disease in 14/60 (23.3%) patients. In astrocytoma, IFS was shorter in patients with PET-PD (median: 10.0 months; 95%CI: 8.3-32.6) compared to PET-SD/-PR/-CR (33.0 months; 95%CI: 22.0-52.1; $p = 0.043$). Similar differences were seen in oligodendroglioma (PET-PD: 16.0 months; 95%CI: 11.7-63.3; vs. PET-SD/-PR/-CR: 34.5 months; 95%CI: 24.3-57.0; $p = 0.036$). At treatment for recurrence, baseline PET showed measurable disease in 37/47 (78.7%) and non-measurable disease in 10/47 (21.3%) patients. PET-CR was seen in 3/47 (6.4%), PET-PR in 16/47 (34.0%), PET-SD in 24/47 (51.1%) and PET-PD in 4/47 (8.5%) patients, with numerical differences in IFS ($p = 0.16$) according to PET response in recurrent disease. In both first-line treatment and recurrence, measurable disease at baseline was not associated with PET response ($p > 0.05$). **Conclusions:** Response assessment based on PET RANO 1.0 criteria is associated with outcome in *IDH*-mutant glioma. Further analyses considering MRI-based response assessment are ongoing for further validation of PET-based clinical trial endpoints. Research Sponsor: European Society for Medical Oncology (ESMO); (awarded to MJM).

Pooled analysis of phase I and expanded access study cohorts of DOC1021 (dubodencel) in combination with chemoradiation for glioblastoma.

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Background: Glioblastoma (GBM) is a poor-prognosis brain malignancy with median overall survival (mOS) of ~12–18 months despite aggressive standard of care (SOC) treatment. DOC1021 is an autologous dendritic cell (DC)-based immunotherapy generated by tandem loading with autologous tumor-derived mRNA and lysate, enabling broad antigen presentation. DOC1021 leverages p38MAPK and mTORC1 signaling cascades to initiate cDC1-like skewing of monocyte-derived DC, leading to potent downstream development of CD8⁺ tissue-homing, cytolytic effector memory cells. **Methods:** This pooled analysis includes newly diagnosed and recurrent IDH-wt patients from two clinical trials (Phase I Study 8148 [NCT04552886] and Expanded Access Protocol EAP0001), treated with DOC1021 after resection and SOC chemoradiation. DOC1021, prepared from mobilized peripheral blood mononuclear cells (PBMC) loaded consecutively with autologous amplified tumor mRNA and tumor lysate, was administered bilaterally near deep cervical lymph node chains every other week for 3 administrations with weekly pegylated-IFN. Study 8148 (n=18) evaluated 4 dose levels (3.5×10^6 to 36×10^6 cells), while Study EAP0001 (n=7) administered only the highest dose level (36×10^6 cells). Patients with subtotal resection or pre-treatment progression were not excluded. Blood was collected before and after DOC1021 to assess peripheral immune responses. **Results:** Among the pooled population (N=25), median age was 58 years (range 47–75), 88% MGMT unmethylated, 24% partially resected, and 16% recurrent disease. There were no dose-limiting toxicities, and a similar safety profile between studies. Common AEs included mild, flu-like symptoms and injection-site reactions. One patient in the EAP study experienced grade 3 cerebral edema after the first DOC1021 dose that fully resolved and subsequent DOC1021 doses were completed per protocol. At the time of analysis, 7 of 21 newly diagnosed patients remain alive ~9–30 months post-surgery. Among recurrent patients (n=4), 2 patients remain alive ~16–20 months after second resection. Pseudo-progression within ~6 months of vaccination was commonly observed. Analysis of post-vaccination PBMC indicated expansion of CD4⁺ (17/20 patients, mean +28.6%, $p=0.0006$) and CD8⁺ (15/20 patients, mean +26.8%, $p=0.001$) central memory T-cell (T_{CM}) compartments as well as substantial upregulation of CD127 expression on circulating CD8⁺ T cells (18/20; mean MFI +72.2%, $p=0.03$). **Conclusions:** Collectively, the data show that DOC1021 plus SOC is well-tolerated, feasible, and potentially efficacious in a challenging population that included subtotal resections, pre-treatment progression, and majority MGMT unmethylated. A multi-center, randomized, open-label Phase 2 trial (NCT06805305) in newly diagnosed GBM is now enrolling to compare DOC1021+SOC vs SOC treatment alone. Clinical trial information: NCT04552886. Research Sponsor: Diakonon Oncology; Cancer Cures 4 Kids.

INB-200: Phase I study and characterization of gene-modified autologous gamma delta ($\gamma\delta$) T cells in newly diagnosed glioblastoma multiforme (GBM).

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Background: Cell therapy for glioblastoma (GBM) holds promise but previous studies have not demonstrated durable responses or improved progression free survival (PFS). We provide updated findings from our assessment of any patients who completed treatment with drug-resistant immunotherapy (DRI) in newly diagnosed GBM. **Methods:** DRI combines the polyclonal upregulation of stress-antigens with concurrent local delivery of MGMT-modified $\gamma\delta$ T cells, engineered to resist temozolomide (TMZ) driven lymphodepletion. The standard-of-care (SOC) chemotherapy TMZ induces transient upregulation of tumor-associated NKG2D-L stress antigens enabling the functional $\gamma\delta$ T cells to identify and eradicate residual cancer cells during the period of maximum tumor vulnerability. Patients received 1×10^7 DRI cells/dose into the resection cavity with 150 mg/m² of IV TMZ on Day 1 of each maintenance cycle. 17 patients received treatment, including 3 who received only a single dose (Cohort 1). 14 patients received repeated doses (3 to 6), (median age 64 (range: 33–75); 93% IDH-WT, 50% MGMT-unmethylated, 57% subtotal resection, KPS 80). 10 contemporaneously enrolled patients treated with SOC only (median age 67 (range: 49–77); 100% IDH-WT, 60% MGMT-unmethylated, 20% subtotal resection, KPS 80) were examined as a control cohort. **Results:** No DLTs, CRS, ICANS or treatment related deaths were reported. As of December 31, 2025, the median PFS for DRI repeat dose patients (N=14) is 13.0 months (m), vs. SOC control (N=10) of 6.6m (+97%) demonstrating prolonged disease control in newly diagnosed GBM. The median overall survival (OS) for repeat dose patients will be updated, as it is still climbing at 17.2m+ vs. SOC control of 13.2m. Notably, 8/14 (57%) of the repeat dose patients had PFS that exceeded their expected OS based on age and MGMT-status, compared to only 1/10 (10%) of SOC control patients. One patient with a grade-4, IDH-mutant tumor remains progression free for 4.6 years with no additional maintenance therapies. Gene expression profiling of pre- and post-manufactured cell products revealed upregulation of cytotoxicity-associated markers of activation and immune cell trafficking (e.g., *IFN- γ* , *GZMB*, *PRF1*). Patient correlate analysis showed that CRS associated serum cytokines *IL-6*, *IL-1 β* , *CCL2*, and *TNF- α* were not increased over baseline during DRI + maintenance-phase TMZ. Peripheral $\gamma\delta$ and total T cell levels, however, improved incrementally with each dose frequency cohort, suggesting an influence on systemic immune reconstitution through local DRI delivery. T cell persistence was demonstrated in recurrent GBM biopsies from patients that revealed significant $\gamma\delta$ T cell infiltration and necrosis well beyond the final dose of TMZ and DRI $\gamma\delta$ T cells. **Conclusions:** These findings demonstrate a manageable safety profile and a positive trend in PFS and OS from treatment with DRI cells. Clinical trial information: NCT04165941. Research Sponsor: IN8Bio, Inc.

Regorafenib in recurrent glioblastoma: Real-world outcomes from a Colombian cohort (REGOMA-COL).

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Background: Therapeutic options for recurrent glioblastoma (GBM) remain limited, with historically poor outcomes following first progression. The phase II REGOMA trial demonstrated an overall survival benefit of regorafenib compared with lomustine, prompting its adoption in selected patients. However, real-world data from Latin America are scarce, where differences in patient characteristics, access to molecular testing, and treatment patterns may influence outcomes. We evaluated the effectiveness and safety of regorafenib in a Colombian cohort of patients with recurrent high-grade gliomas (HGG - WHO 4). **Methods:** REGOMA-COL is a retrospective, single-center cohort study including adult patients with histologically confirmed HGG treated at a tertiary referral center in Bogotá, Colombia. All patients received standard first-line therapy consisting of maximal safe resection followed by IMRT/VMAT with concomitant and adjuvant temozolomide, and subsequently progressed. Regorafenib was administered in the second- or third-line setting at a starting dose of 160 mg daily (3 weeks on, 1 week off), with dose modifications permitted for toxicity. Survival outcomes were estimated using the Kaplan–Meier method. Adverse events were graded according to CTCAE v5.0. Subgroup analyses examined progression-free survival (PFS) by molecular and clinical characteristics. **Results:** Twenty-six patients were included. The median age at diagnosis was 49.3 years, and 80.8% had an ECOG performance status of 1. Most tumors were IDH-wild type (84.6%), and MGMT promoter methylation was present in 38.5%. Regorafenib was administered as second-line therapy in 53.8% of patients and as third-line therapy in 57.7%. Median PFS from regorafenib initiation was 4.9 months (95% CI 3.9–5.7), and median OS from regorafenib was 11.3 months (95% CI 9.3–13.2) (Figure 1). Disease control rate (DCR) with regorafenib was achieved in 69.2% of patients. Toxicity was predominantly low-grade, with fatigue, mucositis, and diarrhea as the most common adverse events. **Conclusions:** In this real-world cohort, regorafenib demonstrated meaningful clinical activity and a favorable safety profile in patients with recurrent HGG. Survival outcomes compared favorably with those reported in pivotal and observational studies, particularly in a relatively young population with preserved performance status. These findings support regorafenib as an important therapeutic option in selected HGG cases and highlight the need for broader Latin American real-world data. Research Sponsor: None.

Lucicebtide (ST101) plus chemoradiation in newly diagnosed GBM patients: Efficacy, pharmacodynamics, and safety from phase 2 window-of-opportunity study.

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Background: Glioblastoma (GBM) is a lethal brain malignancy with no cure. Recurrent GBM (rGBM) is enriched in a mesenchymal-like state, and the tumor microenvironment (TME) is enriched in immune-suppressive tumor-associated myeloid cells (TAMs). C/EBP β is a master regulator of the mesenchymal GBM state and in sustaining immunosuppressive TAMs. Lucicebtide (ST101) is a first-in-class peptide antagonist of C/EBP β with demonstrated anti-tumor activity and TAM reprogramming in preclinical models. **Methods:** The WoO study enrolled 2 cohorts; 9 pts with rGBM that received 2–4 doses of lucicebtide 500mg QW prior to surgery and resumed lucicebtide after surgery to progression and 9 ndGBM pts that received 2–3 doses of lucicebtide 500mg QW prior to surgery and resumed lucicebtide + chemoradiation after surgery until progression. Endpoints include efficacy parameters of PFS and OS, safety as a single agent and in combination with chemoradiation, and pharmacodynamic (PD) analyses including spatial transcriptomics and TME characterization. **Results:** Lucicebtide was well-tolerated alone and in combination with chemoradiation. Tissue analysis indicates BBB penetration, tumor uptake, and C/EBP β target engagement. Lucicebtide + chemoradiation in ndGBM extended PFS beyond historic benchmarks, with the majority of patients remaining on study without progression beyond 21 months. As of January 27, 2026, mOS could not be evaluated; 18- and 24-months OS of 67% and 44% respectively exceeded the historic 39–45% and 26–31% respectively from Stupp 2005 and 2017. In rGBM, lucicebtide improved mPFS of 4.0 months and mOS to 12.3 months, exceeding historical data with chemotherapy (historic mPFS ~ 2 months and mOS 5.6–9.8 months). Spatial transcriptomics revealed significant reductions in C/EBP β regulon activity in tumor cells and macrophages, resulting in a dramatic reduction in the mesenchymal signature in tumor cells. Importantly, lucicebtide altered the infiltration patterns and phenotypes of the TME, including increased effector CD8⁺ infiltration and an increase in the M1/M2 ratio that were associated with disease control. **Conclusions:** Lucicebtide is well-tolerated as monotherapy and in combination with SoC. Improvements in PFS and OS have been seen in GBM patients following lucicebtide exposure. Analysis of tumor resections demonstrate penetration across the BBB and target engagement, and on-target pharmacodynamic activity, including a dramatic reduction in mesenchymal gene signature in tumor cells and a remodeling towards a more permissive immune TME. These data provide the safety, efficacy and mechanistic rationale for continued clinical evaluation of lucicebtide as a novel approach for patients with GBM. Clinical trial information: NCT04478279. Research Sponsor: Ivy Foundation.

Tumor recurrence or treatment effect? Large multi-institutional evaluation of an AI risk assessment model in glioma and brain metastases.

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Background: Distinguishing true tumor recurrence (TuR) from radiation necrosis (RN) on post-treatment MRI scans remains a major neuro-oncology challenge. We hypothesized that an integrated Spatial, Morphologic, and Textural radiomics risk (SMART-risk) model that comprehensively captures local and spatial organization of lesion heterogeneity, can unravel distinct biology across TuR and RN, on clinical MRI; and improve distinction over a data-driven ResNet50 deep learning model. **Methods:** We retrospectively collected multi-institutional post-treatment MRI cohorts: brain metastases (233 studies; from Cleveland Clinic (CCF), University Hospitals Cleveland (UH), University of Wisconsin (UW); and glioma (340 studies from Indiana University (IU), Dana-Farber Cancer Center, Thomas Jefferson University (TJU), and CCF). Over 80% of the studies were pathologically confirmed as TuR or RN. Institution-held-out external testing was performed (metastases: train CCF+UH, test UW; glioma: train IU+TJU+Dana-Farber Cancer Center, test CCF). Following segmentation, 944 radiomic features/lesion were extracted including graph-based spatial organization of tumor heterogeneity (GrRAiL), local gradient texture heterogeneity (COLLAGE), Haralick, and morphology. LASSO-selected features were integrated in a Random Forest classifier. Performance metrics included cross validation accuracy (CV), test accuracy, F1 score, and AUC; interpretability used SHAP. Comparison was performed with a ResNet50 baseline model. **Results:** SMART-Risk demonstrated consistent discrimination on the institution-held-out external test set (Table 1) with ~80% accuracy; ~10-15% improvement over a ResNet50 model. SHAP analysis indicated that features corresponding to spatial organization and local heterogeneity, i.e. average path length, node count and entropy measures, were dominant contributors (Mann-Whitney U test, $p \leq 0.001$). Recurrent tumors showed higher spatial complexity and greater heterogeneity than RN. **Conclusions:** SMART-Risk may provide a noninvasive approach to distinguish TuR from RN on routine post-contrast T1-weighted MRI. By integrating spatial-organization (GrRAiL), texture (COLLAGE/Haralick), and morphology features, SMART-Risk captures complementary signatures and may improve discrimination compared with any single feature family. An AI-based SMART-Risk approach may reduce diagnostic ambiguity, support earlier treatment decisions, and avoid unnecessary invasive procedures. Research Sponsor: NIH / NCI / ITCR; 1U01CA248226-01; NIH / NCI; R01CA277728-01A1; NIH / NCI; 1R01CA264017-01A1; NIH / NCI / ITCR; U01CA248226-03S1.

Test set performance of SMART-Risk vs ResNet50 for TuR vs RN classification.

Cohort (external test site)	Model	CV accuracy	Test accuracy	F1 score	AUC
Metastatic cohort (UW)	SMART-Risk	0.78 ± 0.08	0.79	0.78	0.86
Metastatic cohort (UW)	ResNet50	0.70 ± 0.09	0.60	0.67	0.63
Glioma (CCF)	SMART-Risk	0.83 ± 0.06	0.80	0.84	0.87
Glioma (CCF)	ResNet50	0.69 ± 0.10	0.65	0.77	0.70

Decision support for treatment of patients with glioblastoma: A systems biology approach enabled by explainable AI.

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Background: Glioblastoma (GBM) patients (pts) have median survival of 15 months and 5-year survival <7% with standard therapy. Current clinical decision-making relies on IDH mutation and MGMT methylation status, which provide limited guidance for most pts. We developed SATGBM (SYGNAL Analytics Test for GBM), a systems biology-based test that integrates tumor mutations and gene expression to identify causally dysregulated gene networks and predict treatment response. **Methods:** SATGBM uses Systems Genetics Network AnaLysis (SYGNAL) to mine pts' molecular profiles (RNASeq, WES and NGS) and build disease network maps to single out an individual pt's molecular tumor profile and identify unique causal mechanisms that drive the progression of disease. Treatment predictions integrate network activity scores, deep learning scores, and historical objective response rates from clinical trials. We validated SATGBM in two independent cohorts: (1) 43 pt-derived glioma stem-like cells (PDGSC) screened against 28 anticancer drugs; (2) 83 GBM pts from XCELSIOR open registry observational study with documented treatment outcomes including progression-free survival (PFS) and time on treatment (TOT). **Results:** In PDGSC high throughput screening, SATGBM successfully predicted treatments with greatest drug sensitivity in each of the cell cultures. SATGBM predictions separated responders vs non-responders: median IC₅₀ 2.70×10^{-7} vs 1.00×10^{-3} , Mann-Whitney $p=2.1 \times 10^{-41}$, Pearson $r = -0.38$, AUC = 0.79. In the XCELSIOR cohort (n=31 drug courses), SATGBM correctly predicted the effective response of individual pts to 6 second-line therapies (including off-label drugs). Pts who stayed on SATGBM-recommended treatments remained on therapy 5-times longer compared to predicted non-responders, demonstrating real-world clinical validity and improved outcomes. SATGBM predictions yielded median TOT of 260 vs 50.5 days, $p=0.0021$; sensitivity/specificity were 60.0% / 95.2% and AUC = 0.79 (benefit = ToT ≥ 120 days). **Conclusions:** SATGBM demonstrated statistically significant prediction of treatment outcomes in independent preclinical and clinical validation cohorts. Network-based analysis provided superior predictive accuracy compared to mutation-only or expression-only approaches and provided insights beyond standard GBM biomarkers. These findings support clinical utility of mechanistic network analysis for personalizing GBM treatment decisions and warrant prospective validation in clinical trials. Research Sponsor: U.S. National Institutes of Health; R01-CA259469; U.S. National Science Foundation; NSF-2150265; U.S. National Institutes of Health; R01-NS119650; Washington Research Foundation; Andy Hill Cancer Research Endowment (CARE) Fund; the Burroughs Wellcome Career Award for Medical Scientists; Discovery Grant from the Kuni Foundation; the Ben and Catherine Ivy Foundation; Swedish Medical Center Foundation.

Germline HLA class II diversity as a predictor of survival selectively in MHC-silenced gliomas.

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Background: CD4⁺ T cell help is central to durable anti-tumour immunity and predicts response to neoantigen vaccination. Antigen presentation to CD4⁺ T cells is governed by HLA class II molecules, yet the class II landscape in glioma remains poorly defined. Germline HLA diversity can influence immunity only if tumours retain antigen-presentation capacity. We hypothesised that the prognostic impact of HLA class II heterozygosity in glioma is conditional on tumour MHC-II expression. **Methods:** We performed germline HLA class II typing (DRB1, DQB1, DPB1) in 893 TCGA gliomas (388 glioblastoma, 505 lower-grade glioma) using a weighted consensus of four algorithms (HLA-HD, hla-genotyper, SOAP-HLA, Kourami). Tumour MHC-II expression was quantified using a nine-gene antigen-presentation signature. The primary analysis tested the interaction between germline heterozygosity and tumour MHC-II status on overall survival using multivariable Cox regression. Allele-level survival analyses were exploratory. **Results:** Gliomas showed extensive class II polymorphism (54 DRB1, 28 DQB1, 47 DPB1 alleles), with 35.9% of patients homozygous at one or more loci. The most frequent alleles were DRB1*01 (12.7%), DQB1*03:01 (20.7%), and DPB1*04:01 (38.7%). Germline heterozygosity was not prognostic in unstratified analyses (HR 1.04, 95% CI 0.83–1.32, $p = 0.72$). However, a significant interaction with tumour MHC-II expression was observed (p -interaction = 0.044). In MHC-II-low tumours, germline heterozygosity independently predicted improved survival (HR 0.71, 95% CI 0.52–0.97, $p = 0.031$), whereas no effect was seen in MHC-II-high tumours ($p = 0.89$). Tumour MHC-II expression itself was independently prognostic ($p = 0.004$). Exploratory allele-level analysis identified DRB1*03:01 (10.2%) as nominally associated with worse survival (median 23.7 vs 34.9 months, uncorrected $p = 0.041$). **Conclusions:** Germline HLA class II diversity influences survival in glioma only when tumour antigen presentation is impaired. Combined tumour MHC-II loss and limited germline diversity identify a biologically and clinically high-risk group with compounded antigen-presentation deficits. These findings have direct implications for neoantigen vaccine design and patient stratification, suggesting that restoration of antigen presentation may be required prior to immunotherapy in selected patients. The adverse association with DRB1*03:01 merits mechanistic investigation. Independent validation in 322 glioblastoma patients is ongoing. Research Sponsor: None.

Knowledge distillation for glioma diagnosis: ResNet-based deep learning for WHO grade stratification with real-world deployment optimization.

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Background: Gliomas are the most common primary CNS malignancies. WHO 2021 classification stratifies diffuse gliomas into molecularly-defined grades with vastly different treatment pathways: grades 2–3 (median survival 7–10 years) versus grade 4 glioblastoma (median survival 15 months untreated). Accurate preoperative grading is critical for surgical planning and treatment intensity. However, 5–8% of gliomas are initially misdiagnosed as meningiomas or pituitary adenomas, delaying definitive treatment by 3–6 months. Automated systems achieving high accuracy while remaining deployable in resource-limited settings could substantially reduce diagnostic error. **Methods:** Retrospective cohort: 2,840 brain MRI studies (1,400 gliomas: 700 grade 2–3, 700 grade 4; 900 meningiomas; 540 pituitary adenomas) from six continents. Ground truth used WHO 2021 classification; expert neuroradiologist consensus confirmed diagnoses. ResNet152 (60.2M parameters; 224×224 input; 28.6 GFLOPs) optimized for multi-sequence fusion (T1, T2, FLAIR, post-contrast) served as reference. ResNet18 (11.7M parameters; 224×224 input; 1.8 GFLOPs; 81% parameter reduction) underwent structured knowledge distillation—soft probability targets from ResNet152 with temperature-scaled softmax and regularized cross-entropy loss. Model performance evaluated on accuracy, sensitivity, specificity, F1-score, AUROC. Differential diagnostic accuracy assessed. Deployed globally; 52 neuroradiologists evaluated across six continents. **Results:** Glioma grading: ResNet18 achieved 96.9% accuracy for grade 2–3 vs. grade 4 (sensitivity 97.8%, specificity 96.0%, AUROC 0.991). Differential diagnosis: 95.1% for glioma vs. meningioma; 96.0% for glioma vs. pituitary. External validation confirmed consistent performance (93–97% grading; 94–96% differential diagnosis). Deployment advantage: ResNet18 inference time 38ms/image (ResNet152: 320ms), enabling real-time clinical integration on standard hospital GPU servers. Global deployment: 94.6% of neuroradiologists rated the system clinically valuable. Knowledge distillation preserved 99.2% of teacher diagnostic accuracy while reducing computational cost by 93.7%. **Conclusions:** Knowledge distillation enables ResNet18 to achieve ResNet152-comparable diagnostic accuracy for glioma grading and differential diagnosis while reducing parameters by 81% and computational cost by 94%. This framework solves critical deployment barriers in resource-limited healthcare systems. ResNet18's efficiency enables real-time inference on standard hardware, rapid diagnostic turnaround, and scalable global implementation. This system merits prospective evaluation to reduce time-to-diagnosis and eliminate glioma misclassification worldwide. Research Sponsor: None.

Transcriptomic signature of temozolomide treatment-effect heterogeneity in IDH-wildtype glioblastoma.

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Background: Adjuvant temozolomide (TMZ) is standard of care for IDH-wildtype glioblastoma (GBM), yet clinical benefit is heterogeneous and not fully explained by MGMT promoter methylation. We developed a transcriptomic signature specifically predicting TMZ benefit rather than overall prognosis using a causal inference framework. **Methods:** Transcriptomic and clinical data from 448 patients with histologic grade 4 IDH-wildtype GBM treated with radiotherapy alone or radiotherapy plus TMZ across six cohorts were analyzed. A training set (N=322; TCGA, CGGA-325/693, GLASS) and an independent validation set (N=126; GSE7696, CGGA-301) were used. Data were normalized, batch-corrected, and screened for outliers. To address non-random treatment assignment, inverse probability of treatment weighting (IPTW) based on propensity scores from age, sex, and MGMT status was applied. A 15-gene Temozolomide Sensitivity Score (TSS) was derived using univariate prognostic filtering followed by LASSO modeling of gene-by-treatment interactions. Final gene weights were obtained from a doubly adjusted multivariable Cox model incorporating IPTW and clinical covariates. Performance was assessed by comparing adjusted hazard ratios (HRs) for TMZ benefit across TSS-defined subgroups. **Results:** Five genes emerged as significant independent modulators of TMZ response: C2CD4A, SLC35E3, and DNASE1L3 predicted sensitivity, whereas APOBEC3B and PMAIP1 predicted resistance. In the training cohort, TSS-sensitive patients derived significant benefit from TMZ (median overall survival, 21.0 vs 7.7 months; adjusted HR, 0.20; 95% CI, 0.10–0.39; $P<0.001$), whereas TSS-resistant patients did not (14.4 vs 13.1 months; adjusted HR, 0.89; 95% CI, 0.53–1.51; $P=0.674$), with a significant difference in treatment effect ($P<0.001$). Validation confirmed these findings: TSS-sensitive patients benefited (21.9 vs 12.8 months; adjusted HR, 0.32; 95% CI, 0.16–0.62; $P<0.001$), while TSS-resistant patients did not (13.7 vs 15.1 months; adjusted HR, 1.25; 95% CI, 0.70–2.23; $P=0.453$), showing differential efficacy ($P=0.003$). Age, sex, and MGMT status were balanced between groups. **Conclusions:** A 15-gene transcriptomic signature developed through causal inference and interaction modeling is associated with differential temozolomide benefit in IDH-wildtype glioblastoma independent of MGMT status. This signature may identify patients less likely to benefit from temozolomide, offering a promising tool for de-escalation strategies and enrollment in precision clinical trials. Research Sponsor: None.

Gene–treatment interaction modeling to identify temozolomide-sensitive *IDH*-mutant diffuse gliomas.

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Background: *IDH*-mutant diffuse gliomas are biologically heterogeneous. While radiotherapy is standard, temozolomide (TMZ) is variably used in a risk-adapted manner and preferentially administered to patients with adverse features, introducing substantial indication bias in observational cohorts. Existing molecular markers are largely diagnostic or prognostic rather than predictive of chemotherapy benefit. We aimed to develop a transcriptomic signature identifying differential TMZ benefit while correcting for treatment-selection bias using causal inference. **Methods:** *IDH*-mutant, histologic grade 2–3 glioma patients treated with radiotherapy or radiotherapy + TMZ were analyzed in a training cohort (N=438; TCGA, CGGA325/693) and an independent validation cohort (N=62; CGGA301). To mitigate non-random treatment allocation, inverse probability of treatment weighting (IPTW) was applied using propensity scores from age, sex, histologic grade, 1p/19q codeletion, and MGMT promoter status. A 10-gene temozolomide sensitivity score was derived using univariate filtering followed by LASSO modeling of gene–treatment interactions. Final weights were estimated from a doubly adjusted multivariable Cox model incorporating IPTW and clinical and molecular covariates. Performance was assessed by comparing adjusted hazard ratios (HRs) for TMZ benefit across score-defined subgroups. **Results:** Clinical and molecular baseline characteristics were well balanced between treatment groups. In the training cohort, TMZ-sensitive patients derived significant benefit from TMZ (median overall survival 114.0 vs 85.7 months; adjusted HR 0.58, 95% CI 0.35–0.96; $P=0.035$). In contrast, TMZ-resistant patients demonstrated an elevated adjusted HR (2.98, 95% CI 1.63–5.45; $P<0.001$), consistent with residual confounding from preferential TMZ use in patients with poorer prognosis rather than evidence of treatment harm. A significant difference in treatment effect was observed between subgroups ($P<0.001$). External validation confirmed differential treatment effects: TMZ-sensitive patients showed a concordant trend toward benefit (HR 0.51, 95% CI 0.13–1.94; $P=0.323$), with lack of significance attributable to limited sample size, while TMZ-resistant patients exhibited a resistant trajectory (HR 6.04, 95% CI 1.56–23.38; $P=0.009$), with the difference in treatment effect remaining significant ($P=0.011$). **Conclusions:** Using causal inference and gene–treatment interaction modeling, we developed and validated a 10-gene signature that predicts heterogeneity of TMZ benefit in *IDH*-mutant, histologic grade 2–3 gliomas. This approach distinguishes patients likely to derive substantial benefit from TMZ from those with limited benefit and provides a robust methodological framework for predictive biomarker discovery in non-randomized oncologic datasets. Research Sponsor: None.

Preclinical evaluation of intrathecal TRP1-targeted CAR T cells: Effects on durable antitumor immunity in melanoma leptomeningeal disease.

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Background: Melanoma leptomeningeal disease (LMD) is fatal, with median survival under 3 months and no effective immune-based therapies. Direct cellular immunotherapy of the cerebrospinal compartment has not been systematically explored. Tyrosinase-related protein 1 (TRP1) is a conserved melanocytic lineage antigen expressed across mouse and human melanoma, including CNS involvement. We evaluated the efficacy, durability, and safety of intrathecal TRP1-directed CAR T cell therapy in aggressive melanoma models. **Methods:** TRP1 CAR T cells were generated and evaluated in vitro and in vivo using syngeneic B16 melanoma model, including a leptomeningeal disease setting. CAR T cells were administered intrathecally. Antitumor activity was assessed by bioluminescent tumor burden and survival. Durability of response was evaluated by secondary tumor rechallenge. Toxicity was assessed by longitudinal neurologic monitoring and body weight. Human TRP1 CAR T constructs were evaluated in vitro using real-time cell adhesion (RTCA) assays across multiple donors using TRP1-positive melanoma cell lines to assess antigen-dependent functional activity. scRNAseq data from CSF of melanoma patients were analyzed to determine TYRP1 expression. **Results:** Intrathecal administration of TRP1 CAR T cells resulted in significant tumor control and prolonged survival in aggressive M-LMD models compared with controls (+CTX OS=18%, median survival:18 days; +1x-PBS OS=15%, median survival:17 days). Approximately 40% of treated animals achieved durable remission following intrathecal infusion of CAR Ts (OS=40%, median survival: 32 days, $P<0.0001$). Long-term survivors (eg. more than 60 days) demonstrated functional immune memory, with approximately 36% rejecting secondary tumor rechallenge (OS=36%, median survival: 41 days vs. naïve control OS=17%, median survival: 15 days, $P<0.0001$). Treatment was well tolerated, with no detectable neurologic toxicity or weight loss. RTCA data showed that human TRP1-CAR T cells across donors recognize TYRP1 antigen in target melanoma cells inducing killing. scRNAseq data revealed that 50% of 12 patient samples expressed TYRP1(33,3% were M-LMD, 8.3% were primary intradural spinal melanoma, and 8.3% from 1 autopsy). Surface expression of TYRP1 is being determined using our Rapid Tissue Donation in LMD Core. Together, our data supports translational relevance. **Conclusions:** Intrathecal TRP1-targeted CAR T cell therapy induces potent and durable antitumor immunity in aggressive disease-LMD with a favorable safety profile. These findings represent the first clear demonstration of intrathecal CAR T cell therapy in melanoma LMD and establish proof of concept for CNS-directed CAR T strategies targeting a melanocytic lineage antigen. This work provides a rational foundation for systematic optimization and IND-enabling development. Research Sponsor: None.

Efficacy of high-dose chemotherapy in adult patients with relapsed or refractory medulloblastoma.

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Background: Adult medulloblastoma (MB) is rare, and there is no standard salvage approach for relapsed or refractory cases. High-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) has shown potential, but evidence in adults remains limited. This study evaluated the response rate, survival and toxicity after HDC with ICE regimen followed by ASCT in MB, with further focusing on post-ASCT response and pretransplant intracranial residual disease (ICRD). **Methods:** We retrospectively analyzed adult patients with relapsed/refractory MB who underwent HDC with the ICE regimen followed by ASCT. Baseline features, treatment response, progression-free survival (PFS), overall survival (OS), and treatment-related toxicity were evaluated. Subgroup analyses focused on post-ASCT response and pretransplant intracranial residual disease (ICRD). **Results:** The study included 23 patients (median age: 24 years; male: 52%, with 43% classic subtype and 61% pretransplant ICRD). The overall and complete response (CR) rates to HDC was 73.9% and 48%, respectively. The median PFS was 12.8 months, and OS was 45.1 months, with 2-year PFS and OS rates of 31% and 63%, respectively. Patients achieving CR after ASCT had significantly longer OS (NR vs 16.4 months; HR, 0.15; 95% CI, 0.03–0.72; $P=0.02$), corresponding to an 85% reduction in mortality risk compared with non-CR patients. OS was markedly shorter in patients with pretransplant intracranial residual disease compared with those without (22.5 vs. 74.0 months; HR, 7.08; 95% CI, 1.3–36.3; $p=0.008$). The large cell/anaplastic subtype remained the poorest prognostic group despite ICE induction. Toxicity was dominated by universal grade 4 myelosuppression and febrile neutropenia, but no transplantation-related mortality occurred. **Conclusions:** This study showed that HDC with ICE followed by ASCT is feasible in adults with relapsed/refractory MB, with encouraging survival and manageable toxicity. Pretransplant ICRD clearance and achievement of CR were major prognostic determinants, while non-CR patients remained at high risk, highlighting the need for treatment intensification in this subgroup. Research Sponsor: None.

Molecular characterization of WHO grade II atypical meningioma using the AACR Project GENIE database.

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Background: Atypical meningioma (AM) is a WHO grade II neoplasm arising from meningeal arachnoid cap cells and is distinguished from WHO grade I meningiomas by parenchymal invasion and rapid proliferation. AM demonstrates recurrence rates up to 52% following gross total resection and >90% after subtotal resection. The absence of FDA-approved systemic treatments for AM underscores the need to define oncogenic drivers for targeted therapies. This study leverages the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) database to characterize the genomic landscape of AM and identify key genetic drivers for therapeutic targets. **Methods:** The AACR GENIE database was accessed from cBioPortal (v18.0-public) on December 12, 2025 to identify all AM patient samples. Fisher's exact test and non-parametric tests (Mann-Whitney U) were used with Benjamini-Hochberg False Discovery Rate correction to analyze most common genetic mutations, demographic correlations, and mutual exclusivities. Unknown values were excluded from analysis. **Results:** The cohort identified 402 AM samples from 394 patients. The cohort was slightly female-predominant (52.8%) and largely adult (94.0%). Most patients were White (47.2%), followed by Asian (7.4%) and Black (3.6%). Most samples (n=307, 76.4%) were primary tumors and 48 (11.9%) were metastatic. *NF2* was the most prevalent mutation (n=228; 56.7%), followed by *TERT* promoter mutations (n=52; 12.9%). Chromatin-modifying genes, including *KMT2D* (n=24; 6.0%), *KMT2A* (n=19; 4.7%), and *KMT2C* (n=16; 4.0%), were frequently altered. Additional recurrent mutations were observed in *SPTA1* (n=21; 5.2%), *MT-ND5* (n=20; 5.0%), *FAT1* (n=20; 5.0%), *PRKDC* (n=18; 4.5%). Sex-stratified analysis revealed male-exclusive mutations in *DAXX* (n=9), *IL6ST* (n=4), *TMPRSS2* (n=4), *SMARCE1* (n=4), and *COL2A1* (n=5) that reached statistical significance (all $p < 0.05$). *TSC2* and *DNMT3A* mutations were significantly more frequent in males, whereas *BRCA1* mutations were uniquely observed in females ($p < 0.05$). *NF2* mutations were enriched in Asian patients ($p < 0.001$), while *TERT*, *KDR*, *PTPRB*, *SPEN*, and *KMT2C* were enriched in Black patients (all $p < 0.05$). *NF2* and *TERT* demonstrated significant mutual exclusivity ($p < 0.05$). Co-occurrence was observed between *ROS1/ATM* and *KMT2D/TSC2* ($p < 0.05$). Metastatic tumors were enriched for *BRCA1*, *IKBKE*, and *PALB2*, with *MDM4* exclusive to metastatic disease ($p < 0.001$). **Conclusions:** To our knowledge, this is the first GENIE study to identify *NF2* and *TERT* as central genomic drivers of AM, with their observed mutual exclusivity suggestive of divergent oncogenic pathways. Race-associated mutations, such as enrichment of *NF2* in Asian patients and *TERT* in Black patients, emphasize demographic consideration in targeted therapies. These findings prioritize *NF2* and *TERT* as targets for precision therapeutics in AM. Research Sponsor: None.

Long term outcomes of central neurocytoma in a multi-institutional cohort: The role of radiotherapy and Ki-67.

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Background: Central neurocytomas (CNs) are rare, WHO grade 2 brain tumors that can have relatively high recurrence rates following surgical resection. Owing to the rarity of CNs and limited robust data, the optimal use and timing of radiotherapy (RT) remain undefined, particularly in young adults with low mortality. Tumor proliferation index (Ki-67) may also predict CN recurrence rates, but there is no consensus on its utility in clinical practice. The present collaboration between Northwestern University and the Mayo Clinic describes long-term outcomes of CN as it relates to RT timing and Ki-67 level. **Methods:** Patients established between 1990–2025 with a tissue diagnosis of CN at Northwestern University and the Mayo Clinic were reviewed. Demographic, treatment, and tumor characteristics (histologic/molecular) were recorded. Recurrence free survival (RFS) and overall survival (OS) were calculated according to the Kaplan Meier–method. **Results:** Fifty-one patients with CN (51% male, 49% female)–with a median age of 26 years and 9.7 years median follow-up–were included. RFS at 2, 5, and 10 years for the cohort was 79%, 65%, and 59% respectively; OS at 10 years for the cohort was 94%, and no deaths were attributed to uncontrolled CN. Subtotal resection (STR) yielded 2- and 5-year RFS of 74% and 65%, while gross total resection (GTR) yielded 2- and 5-year RFS of 90% and 66%. Median Ki-67 of the cohort was 3%; RFS at 2 and 5 years for Ki-67 <3% was 82% and 76%, compared to 76% and 43% for Ki-67 ≥3% (p<0.02). In patients who underwent resection without adjuvant RT (n=35), those with STR had a 2- and 5-year RFS of 61% and 45%, and those with GTR had a 2- and 5- year RFS of 88% and 61%. Additionally, without adjuvant RT, RFS at 2 and 5 years for Ki-67 <3% was 73% and 64% versus 71% and 24% for Ki-67 ≥3%. Among patients without adjuvant RT and Ki-67 ≥3% (n=14), 2-year RFS was 60% after STR and 78% after GTR. Salvage RT after first recurrence (n=16) had a 5-year RFS of 81%, with a median follow-up of 4.1 years. **Conclusions:** We report one of the largest cohorts of CN with long-term follow-up. STR and/or Ki-67 ≥3% were associated with shorter RFS. Salvage RT at recurrence achieved durable long-term tumor control, and long-term (~10-year) mortality was low. In appropriately selected patients, observation after resection may be a reasonable initial strategy, with RT reserved for salvage. Research Sponsor: None.

General cohort characteristics (n=51) with Ki-67 (n=39).	
Variable	Number (%)
Median Age (years)	26 (range: 5-57)
Gender, Male:Female (M/F)	26:25 (51/49)
Subtotal Resection	29 (57)
Gross Total Resection	22 (43)
Adjuvant Radiotherapy	16 (31)
Salvage Radiotherapy	16 (31)
No Radiotherapy	19 (38)
Ki-67 ≥3	21 (56)
Ki-67 <3	18 (44)

Final results of a single-arm, open-label, multicenter phase 2 study of the radio-pharmaceutical [^{177}Lu]Lu-DOTA-TATE and [^{68}Ga]Ga-DOTA-TATE in adults with advanced intracranial meningioma.

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Background: A subset of meningiomas has an aggressive clinical course requiring multimodal therapies. Yet, treatment options beyond surgery and radiation are limited. Somatostatin receptor 2 (SSTR2) is uniformly expressed in meningiomas and can be targeted by the radio-pharmaceutical agent [^{177}Lu]Lu-DOTA-TATE (^{177}Lu -Dotatate). [^{68}Ga]Ga-DOTA-TATE (^{68}Ga -Dotatate) PET is emerging as a promising imaging modality to assess treatment response in SSTR2-expressing tumors. However, prospective clinical data supporting the use of ^{177}Lu -Dotatate and ^{68}Ga -Dotatate in treatment-refractory meningiomas is limited. **Methods:** In this multicenter, open-label, phase 2 clinical study (NCT03971461), adult patients with progressive intracranial meningiomas received ^{177}Lu -Dotatate at 7.4 GBq (200 mCi) every 8 weeks for 4 doses. The primary endpoint was 6-month progression-free survival (PFS-6). Up to 5 meningioma lesions per patient were assessed by gadolinium-enhanced T1 MRI every 12 weeks. ^{68}Ga -Dotatate PET was obtained before/after ^{177}Lu -Dotatate treatments. Lesional ^{68}Ga -Dotatate PET activity was assessed relative to liver/spleen or superior sagittal sinus (SSS). **Results:** 32 patients (female = 21, male = 11) with progressive meningiomas (WHO grade 1 = 7, grade 2 = 24, grade 3 = 1) were enrolled. Median age was 65.5 (range 41-78) years. All patients had at least one prior tumor surgery and at least one course of radiation. Overall, ^{177}Lu -Dotatate was well tolerated and the most common grade 3/4 adverse events were transient cytopenia in 15 patients (47%). One patient (3%) discontinued treatment due to grade 4 thrombocytopenia. PFS-6 was reached in 22 patients (69%), which includes 5 of 7 (71%) with grade 1 and 17 of 24 (71%) with grade 2 meningiomas. Best radiographic response by MRI was partial response (PR) in 5 (16%) and stable disease (SD) in 20 (63%) patients. Eight patients (16 lesions) were evaluable by paired MRI and ^{68}Ga -Dotatate PET pre- and post-treatment. Referenced to SSS, ^{68}Ga -Dotatate avidity reduced by $\geq 50\%$ in 2 lesions (PR), 25-49% (minor response, MR) in 3 lesions and remained stable (< 25% reduction and < 25% increase) in 11 lesions. Using liver/spleen as a reference (6 patients, 14 lesions), ^{68}Ga -Dotatate uptake was reduced in 9 lesions and stable in 5 lesions. ^{68}Ga -Dotatate PET assessments were generally concordant with MRI-based treatment response assessments. **Conclusions:** The primary endpoint (PFS-6) was met in this phase 2 study with 69% of patients achieving PFS-6, thereby surpassing established historical benchmarks. ^{177}Lu -Dotatate was generally well tolerated and deserves further study in patients with advanced meningiomas. Exploratory ^{68}Ga -DOTATATE PET studies showed decreased uptake in a subset of lesions and bears promise as an imaging biomarker to assess treatment response. Clinical trial information: NCT03971461. Research Sponsor: None.

Long-term outcomes of CNS lymphoma patients treated with glucarpidase.

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Background: High-dose methotrexate (HD-MTX) is the backbone of potentially curative therapy for central nervous system lymphoma (CNSL) but requires inpatient admission for hydration and monitoring to minimize toxicity. Glucarpidase is a recombinant bacterial enzyme that rapidly clears systemic MTX without crossing the blood-brain barrier. It is FDA-approved as a rescue agent in the setting of MTX toxicity. Exploration of use beyond this indication has been limited, in part, due to concerns about immunogenicity and effect on MTX efficacy. We previously demonstrated the safety of repeated low-dose glucarpidase. Here, we report long-term outcomes of CNSL patients treated with MTX and glucarpidase on clinical trial NCT03684980. **Methods:** NCT03684980 is a multicenter, open-label trial that prospectively enrolled primary (PCNSL) or secondary (SCNSL) lymphoma patients across different cohorts to receive repeated doses of MTX (3–8 g/m²) and glucarpidase (1000–2000u). Patients who received ≥ 6 of 8 planned doses were included. Patients had indication for MTX for newly diagnosed (ND) or relapsed/refractory (r/r) disease. There were no restrictions on post-MTX therapy or consolidation. Objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) were assessed. **Results:** Twenty-two enrolled patients met inclusion criteria; 10 (45%) were women. Median age was 70 years, and median Karnofsky Performance Status was 80. PCNSL accounted for 20/22 (91%) of cases; 5/22 (23%) were treated for r/r disease. Following MTX-based induction, patients achieved complete response (CR) (n=10, 45%), CR unconfirmed (n=2, 9%), partial response (n=6, 27%), stable disease (n=2, 9%), or progressive disease (n=2, 9%) for an ORR of 18/22 (82%). Responding patients received consolidation with cytarabine (n=10), autologous stem cell transplant (ASCT) (n=5), ibrutinib maintenance (n=1), or unknown (n=2). Median follow-up was 55.5 months. Median PFS and OS were not reached overall. PFS and OS were not reached for PCNSL, versus 7.3 and 21.0 months for SCNSL. PFS was not reached for ND patients versus 12.4 months for patients with r/r disease; OS was not reached for either group. **Conclusions:** Repeated low-dose glucarpidase does not appear to adversely impact long-term outcomes in CNSL. Outcomes were superior in PCNSL and ND disease compared to SCNSL and r/r disease. These findings support further exploration into the use of glucarpidase to facilitate MTX clearance without compromising efficacy. Clinical trial information: NCT03684980. Research Sponsor: None.

Phase I trial of trastuzumab deruxtecan in combination with stereotactic radiosurgery for brain metastases from HER2-positive breast cancer.

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Background: Brain metastases (BM) develop in nearly 40–50% of patients with HER2-positive breast cancer. Stereotactic radiosurgery (SRS) provides effective local control of treated lesions but does not prevent the development of new BM, while whole-brain radiation therapy is associated with significant neurocognitive toxicity. Trastuzumab deruxtecan (T-DXd) is a HER2-targeted antibody-drug conjugate (ADC) that has demonstrated significant systemic and intracranial activity in patients with HER2-positive breast cancer. Preclinical and clinical data suggest that combining HER2-directed therapy with radiation may enhance intracranial disease control. However, there is conflicting information about the rate of radiation necrosis in patients treated with T-DXd and SRS. We hypothesize that the combination of T-DXd and stereotactic radiosurgery may be safe and provide effective intracranial disease control in patients with HER2-positive breast cancer BM. **Methods:** This is a prospective, single-arm, multicenter, open-label, ongoing phase I clinical trial evaluating the safety, tolerability, and maximum tolerated dose of T-DXd in combination with SRS in patients with BM from HER2-positive breast cancer. Eligible participants are adults (≥ 18 years) with histologically confirmed HER2-positive breast cancer, Eastern Cooperative Oncology Group performance status of 0–2, adequate organ function, and 1–10 newly diagnosed BM who are candidates for SRS. Any number of prior systemic therapies is permitted, except prior exposure to T-DXd. Key exclusion criteria include leptomeningeal metastases, clinically significant intra- or peri-tumoral hemorrhage, prior cranial radiation therapy, active or prior interstitial lung disease or pneumonitis, and BM within 5 mm of the optic apparatus. Participants receive SRS to all eligible lesions with concurrent intravenous T-DXd every 3 weeks. A standard 3+3 dose de-escalation design is used, starting at 5.4 mg/kg with planned de-escalation to 4.4 mg/kg and 3.2 mg/kg. Dose-limiting toxicities are assessed during a 3-week post-SRS evaluation period. The primary endpoint is safety, tolerability, and determination of the maximum tolerated dose. Secondary endpoints include intracranial and extracranial progression-free survival, overall survival, and objective response rate assessed by RECIST v1.1. Exploratory endpoints include intracranial response assessed using RANO-BM criteria and longitudinal changes in neurocognitive function. Upon determination of the maximum tolerated dose, an expansion cohort will enroll up to 20 participants. The trial has been approved by the Institutional Review Board and is currently enrolling participants. Research Sponsor: None.

Randomized phase 2 trial of ruxolitinib in combination with radiation and temozolomide compared to radiation and temozolomide for newly diagnosed glioblastoma.

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Background: Glioblastoma is associated with poor outcomes despite treatment with radiation and temozolomide. Therapeutic resistance and disease recurrence are driven in part by glioma stem cell populations and activation of oncogenic signaling pathways, including the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. Aberrant JAK/STAT signaling has been implicated in tumor proliferation, stem cell maintenance, immune modulation, and resistance to radiation and alkylating chemotherapy in glioblastoma in preclinical models. Ruxolitinib is an oral JAK1/2 inhibitor with established clinical use in myeloproliferative neoplasms. Preliminary activity has also been reported in high-grade glioma; in the phase 1, non-randomized CRUX study. **Methods:** This is a randomized, multicenter, open-label, ongoing phase II clinical trial enrolling adults (≥ 18 years) with newly diagnosed, histologically confirmed IDH-wildtype glioblastoma and Karnofsky performance status ≥ 70 . Eligible patients must have adequate organ function and available tumor tissue for molecular characterization. Participants are randomized 1:1 and stratified by MGMT promoter methylation status, performance status, sex, and extent of resection. Patients assigned to the experimental arm receive oral ruxolitinib 20 mg administered twice daily in combination with standard radiation therapy (60 Gy delivered in 30 fractions) and concurrent temozolomide at 75 mg/m², followed by adjuvant temozolomide at 150–200 mg/m² with continuous ruxolitinib at 20 mg bid. Patients in the control arm receive radiation therapy with concurrent and adjuvant temozolomide per standard of care. Treatment continues until disease progression, unacceptable toxicity, withdrawal of consent, or completion of protocol-defined therapy. The primary endpoint is overall survival (OS). Secondary endpoints include progression-free survival (PFS), objective response rate (ORR), duration of response (DOR), and safety. Tumor response is assessed using modified Radiologic Assessment in Neuro-Oncology (mRANO) criteria. Exploratory objectives include correlative analyses evaluating tumor tissue biomarkers associated with treatment response or resistance. The planned sample size is 190 participants across multiple institutions in the United States. The statistical analysis is a sequential design with one interim look at 50% events on one-sided log rank test, an overall sample size of 172 participants (86 in the control group and 86 in the treatment group) needed to achieve 80 % power at a 0.1 significance level to detect a hazard ratio of 0.68182 when the control group median survival time is 15 months. The trial has been approved by the Institutional Review Board (IRB) and is currently enrolling patients. Clinical trial information: NCT06991101. Research Sponsor: None.

CLARITY-GBM: A phase II, multi-centered, open-label, single-arm study to evaluate the safety and efficacy of cetuximab and lomustine (CCNU) in adult patients with recurrent high-grade glioblastoma.

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Background: Recurrent glioblastoma (GBM) has a poor prognosis with no universally accepted systemic standard of care. Lomustine (CCNU) remains a commonly used benchmark, achieving 6-month progression-free survival (PFS-6) rates of approximately 20%. Epidermal growth factor receptor (EGFR) amplification is present in a substantial proportion of GBMs and represents a biologically relevant therapeutic target. Cetuximab, an anti-EGFR monoclonal antibody, has demonstrated preclinical activity and limited clinical efficacy in EGFR-driven high-grade gliomas. CLARITY-GBM evaluates the safety and preliminary efficacy of combining cetuximab with lomustine in adults with recurrent high-grade glioblastoma. **Methods:** CLARITY-GBM is a prospective, open-label, multicenter, single-arm Phase II study conducted at four tertiary cancer centres in India. Eligible patients are adults (≥ 18 yrs) with histologically confirmed WHO grade 4 glioblastoma at first or second recurrence following standard chemo-radiation, ECOG performance status 0–2, and measurable disease per RANO criteria. Participants will receive cetuximab intravenously 500 mg/m² every 2 weeks in combination with oral lomustine 110 mg/m² every 6 weeks. Treatment continues until disease progression, unacceptable toxicity, withdrawal of consent, or investigator decision. Tumour assessments are performed every 6 weeks using MRI and evaluated according to RANO criteria. The study uses an exact single-stage Phase II design testing the null hypothesis that $PFS-6 \leq 20\%$ versus the alternative hypothesis that $PFS-6 \geq 40\%$, with a one-sided alpha of 0.10 and 80% power. A total sample size of 25 patients is planned to ensure 24 evaluable patients for the primary analysis. The regimen will be considered promising if at least 8 patients are progression-free at 6 months. A single interim futility analysis is planned after 15 evaluable patients. The primary endpoint is PFS-6. Secondary endpoints include progression-free survival, overall survival, objective response rate, duration of response, safety and tolerability (CTCAE v5.0), corticosteroid-sparing effect, and health-related quality of life (EORTC QLQ-C30 and BN20). Exploratory analyses evaluate correlations with EGFR amplification, EGFRvIII status, and MGMT promoter methylation. Clinical trial information: CTRI/2026/01/100794. Research Sponsor: None.

Design and key methodological features of the CLARITY-GBM trial.	
Characteristic	Description
Study Design	Phase II, open-label, single-arm
Population	Adults with recurrent WHO grade 4 GBM
Sample Size	25 planned (24 evaluable)
Treatment	Cetuximab q2w + Lomustine q6w
Primary Endpoint	PFS-6
Statistical Design	One-sample exact binomial
Null/Alternative	$PFS-6 \leq 20\%$ vs $\geq 40\%$
Power/Alpha	80%, one-sided 0.10
Interim Analysis	After 15 evaluable patients
Exploratory Biomarkers	EGFR, EGFRvIII, MGMT

TTFIELDS with maintenance temozolomide (TMZ) and pembrolizumab versus TTFIELDS with maintenance TMZ and placebo for newly diagnosed glioblastoma: The phase 3 EF-41/KEYNOTE D58 trial.

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Background: Glioblastoma remains a lethal disease with limited treatment options. With current standard-of-care, consisting of maximal safe resection followed by radiotherapy with concurrent TMZ, then maintenance TMZ plus TTFIELDS, median overall survival (OS) is 20.9 months, as reported in the pivotal EF-14 trial completed more than a decade ago. While immune checkpoint inhibitors (ICIs) have improved outcomes in multiple malignancies, they have not demonstrated meaningful clinical benefit in glioblastoma, in part because the tumor microenvironment (TME) is typically profoundly immunosuppressive. Strategies that reprogram the TME toward immune activation may therefore enable ICIs to elicit more effective anti-tumor immunity. Beyond antimitotic effects, TTFIELDS have shown preclinical evidence of inducing immunogenic cell death and activating type 1 interferon signaling via DNA sensor inflammasomes, with downstream increases in dendritic cell activation and cytotoxic T cell infiltration. In a single-arm phase 2 study (NCT03405792), TTFIELDS plus TMZ and pembrolizumab was associated with improved progression-free survival (PFS) and OS compared to historical controls in newly diagnosed glioblastoma. Here, we describe the design of a randomized phase 3 trial evaluating this regimen. **Methods:** EF-41/KEYNOTE D58 is a randomized, double-blind, placebo-controlled, phase 3 study (NCT06556563). Eligible patients have newly diagnosed glioblastoma (WHO 2021 Classification), have completed concurrent chemoradiotherapy, and can initiate treatment 4–7 weeks thereafter. Additional criteria include ECOG performance status 0–1 and availability of tumor tissue for central MGMT methylation analysis. Key exclusion criteria include prior anti-PD(L)1 or anti-PDL2 therapy and ongoing dexamethasone >2 mg/day. Patients are randomized 2:1 to TTFIELDS (200 kHz for ≥ 18 hours/day) plus maintenance TMZ (150–200 mg/m²/day PO, days 1–5 of each 28 day cycle for 6–12 cycles) with either pembrolizumab 200 mg IV Q3W (up to 35 cycles) or matching placebo. TTFIELDS is continued until second progression. At first progression, TTFIELDS therapy is maintained and patients may receive standard salvage therapy, including re-resection and/or radiotherapy as well as systemic therapy. The target enrollment is 741 patients, providing 85% power to detect an OS improvement at a two-sided alpha of 0.05 using a 2-sided log-rank test. The primary endpoint is OS. Secondary endpoints include PFS per RANO 2.0 and RANO, PFS6 and PFS12 rates (RANO 2.0), PFS2 (RANO 2.0), 1- and 2-year survival rates, EORTC QLQ-C30 with BN20 module score, and safety. MRI assessments are performed every 9 weeks and evaluated per RANO 2.0. Adverse events are monitored throughout the study. Enrollment is ongoing. Clinical trial information: NCT03405792. Research Sponsor: None.

Resection and intracranial implant of (Z)-*n*-butylidenephthalide wafer followed by temozolomide as treatment for recurrent glioblastoma: A randomized phase IIb/III trial.

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Background: Glioblastoma, an isocitrate dehydrogenase (IDH)–wildtype diffuse glioma, remains highly lethal despite standard therapy, and the absence of an effective treatment at recurrence highlights a critical unmet clinical need. (Z)-*n*-butylidenephthalide ((Z)-BP) is a multimodal anti-glioblastoma agent that inhibits key mechanisms mediating oncogenic signaling including epidermal growth factor receptor (EGFR), AXL-1 receptor, and c-mesenchymal epithelial transition factor (c-Met) receptor, as well as DNA repair (MGMT) and immune suppression (programmed death-ligand 1, PD-L1). To enable sustained local delivery of (Z)-BP, an interstitial controlled-release polymer wafer was developed and advanced through Phase I and Phase IIa evaluation, demonstrating feasibility, a favorable safety profile, and early indications of survival signals. Building on these findings, a randomized Phase IIb/III study has been initiated to further evaluate intracranial (Z)-BP implantation using this controlled-release platform. **Methods:** The trial (NCT07349693) is an open-label, randomized study that aims to determine the efficacy of tumor resection with implantation of the (Z)-BP wafer, followed by temozolomide treatment in the setting of recurrent glioblastoma. With a sample size of 175, the study is designed to observe 116 overall survival events to achieve 80% power. Eligible adults must have histologically confirmed glioblastoma at first or second recurrence following standard first-line therapy and maintain a Karnofsky Performance Status ≥ 70 . Furthermore, candidates require measurable disease per response assessment in neuro-oncology (RANO) 2.0 criteria (lesion ≥ 1 cm) that is deemed suitable for gross total resection. Subjects are excluded if they present with oligodendroglioma, mixed glioma, specific genetic markers (IDH or H3K27M mutations, 1p19q co-deletion), or prior bevacizumab treatment with uncontrollable progression. Patients with MRI findings showing multi-focal disease, diffuse dissemination, lesions > 6 cm, or tumor locations deemed unsuitable for safe resection and wafer implantation will also be excluded. Subjects are randomized in a 2:1 ratio to either resection with 6 (Z)-BP wafers implantation or resection only (control arm). All enrolled patients subsequently receive six cycles of temozolomide. The primary endpoint is median overall survival (OS). Secondary endpoints include progression-free survival (PFS), OS and PFS rates at 6, 9, 12, 18, and 24 months, and objective response rate (ORR, based on RANO 2.0). Exploratory objectives include assessing plasma concentrations of (Z)-BP and its metabolite, quality of life (EORTC QLQ-C30), and survival analyses stratified by molecular subgroups (EGFR, AXL, c-Met, MGMT, and PD-L1 expression). The enrollment is expected in Q2 2026. Clinical trial information: NCT07349693. Research Sponsor: Everfront Biotech.

Randomized phase 2 study to evaluate the efficacy and safety of silevertinib in combination with temozolomide in newly diagnosed patients with EGFRvIII-positive IDHwt MGMT unmethylated glioblastoma.

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Background: Targeted therapy for patients with newly diagnosed glioblastoma (ND-GBM) has made little progress. First-line therapy remains surgery, adjuvant radiotherapy with temozolomide (TMZ), and maintenance TMZ. This treatment paradigm is even less effective for the ~60% of patients with MGMT unmethylated status. Oncogenic epidermal growth factor receptor (EGFR) alterations are identified in ~50% of ND-GBM tumors irrespective of MGMT status. EGFRvIII is present in ~30% of ND-GBM and is nearly always expressed with other EGFR mutations and/or EGFR amplification. Prior clinical trials of EGFR targeting drugs have shown limited benefit primarily due to poor CNS penetrance and/or lack of potency across EGFR variants and EGFR amplification. Silevertinib (BDTX-1535) is a 4th generation covalent EGFR tyrosine kinase inhibitor (TKI) with high CNS penetrance targeting the full spectrum of oncogenic EGFR alterations in GBM, including variants (EGFRvIII, vII, vVI), mutations, and amplification. Silevertinib has shown additive antitumor effects with TMZ in an intracranial GBM tumor model expressing EGFRvIII with EGFR amplification. A phase 0/1 window-of-opportunity study in patients with recurrent GBM showed that silevertinib reached therapeutic levels in infiltrative GBM tissue with associated biomarker suppression (NCT06072586). Silevertinib was well tolerated and demonstrated promising clinical activity in a phase 1 study in patients with recurrent GBM (ASCO 2024). This randomized phase 2 study will evaluate efficacy and safety of silevertinib in combination with TMZ in adults with EGFRvIII-positive (EGFRvIII) unmethylated MGMT ND-GBM. **Methods:** This multicenter study (NCT05256290) will be conducted in the US and consists of 2 sequential parts. Part 1 (Safety Run-in) will enroll up to 12 patients to evaluate the safety of two doses of silevertinib (150mg QD, 200mg QD) in combination with TMZ and will inform the selected dose for Part 2. In Part 2 (Efficacy Evaluation), patients will be randomized 1:1 to receive adjuvant silevertinib in combination with TMZ or TMZ alone. Patients with EGFRvIII ND-GBM who have completed surgery and adjuvant chemoradiation are eligible (Table). The primary endpoint for Part 2 is progression free survival by blinded independent central review using Response Assessment in Neuro-Oncology (RANO2.0) criteria. Clinical trial information: NCT05256290. Research Sponsor: Black Diamond Therapeutics.

Key inclusion criteria.

Surgically resected and histologically proven ND-GBM
 Tumor EGFR status by local test using commercially available or CLIA certified assay
 Part 1: any pathogenic EGFR alteration
 Part 2: EGFRvIII-positive by NGS
 Unmethylated MGMT tumor status (Part 2 only)
 No treatment for ND-GBM other than surgery followed by chemoradiation
 ≥4 weeks after chemoradiation therapy with post-radiation MRI showing no progression

Targeting macrophage migration inhibitory factor: A phase 2 and pharmacodynamic study of sitagliptin in patients with progressive grade 4 gliomas.

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Background: One mechanism of immunosuppression in the glioblastoma (GBM) microenvironment involves systemic and local accumulation of myeloid-derived suppressor cells (MDSCs) that inhibit cytotoxic immune cell populations and contribute to immune suppression. GBM patients have increased circulating MDSCs compared to lower grade glioma patients, and GBM patients with a better prognosis have reduced MDSCs in their tumors as well as in their peripheral circulation. A trial (NCT02669173) performed at the Cleveland Clinic demonstrated that pre-surgical anti-MDSC therapy (capecitabine) was associated with reduced circulating MDSCs and increased cytotoxic immune infiltration in tumor tissue. This proof-of-principle pilot study demonstrated that targeting MDSCs in patients can attenuate tumor-induced immunosuppression. Subsequent work at the Cleveland Clinic demonstrated that MDSCs require dipeptidyl peptidase 4 (DPP-4) for entry into the brain and overall MDSC function. Screening for a DPP-4 inhibitor identified sitagliptin as a good inhibitor with limited toxicity with efficacy in pre-clinical models. Hypothesis: Treat of GBM patients with sitagliptin will deplete circulating MDSCs and reduce their entry into the brain, reversing systemic and intratumoral immunosuppression. To test this hypothesis, we plan a “window of opportunity” clinical trial to evaluate the safety and biological impact of sitagliptin treatment in patients with recurrent grade 4 glioma undergoing clinically indicated surgical resection. **Methods:** For this trial, we will randomize 48 patients: 36 will receive pre- and post-operative treatment with sitagliptin and 12 will receive post-operative sitagliptin alone. All patients will receive post-operative sitagliptin and chemotherapy until disease progression. Primary endpoint: Difference in tumor CD8+ T cell count between the participants randomized to pre-surgical sitagliptin versus the participants randomized to no pre-surgical treatment. Secondary endpoints: PFS₆, OS₁₂, and safety. Exploratory endpoints: peripheral and intratumoral immune profiling for assessment of TAMs, MDSCs, and CD8+ T cells; tumor radiomic features on MRI brain pre-surgery that might predict intratumoral and peripheral CD8+ T cell count and peripheral MDSC levels; peripheral blood cytokine and immune gene expression profiling for increase in immune activation signatures. This is a window-of-opportunity trial of sitagliptin for patients with grade 4 gliomas to test the hypothesis that sitagliptin, a DPP-4 inhibitor, can reduce MDSC activity, enhance immune activation, and thereby increase the quantity of tumor infiltrated CD8+ T cells. These improvements in immune suppression, combined with chemotherapy will hopefully increase PFS and OS for patients. Clinical trial information: NCT07003542. Research Sponsor: None.

A trial to evaluate CSF ctDNA and safety of plixorafenib alone or with retifanlimab in patients with BRAF-altered glioma.

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Background: BRAF V600E mutant gliomas are difficult to treat in the recurrent setting due to adaptive resistance to FDA-approved targeted therapies. Emerging therapeutic approaches include novel BRAF inhibitors or combination therapies, but evaluating treatment response is limited by radiographic techniques and the infeasibility of serial tissue sampling. This two-arm study will evaluate the feasibility of using CSF and plasma circulating tumor DNA (ctDNA) as biomarkers for response to a novel-BRAF inhibitor, plixorafenib alone or in combination with PD-1 inhibitor, retifanlimab. Plixorafenib is a small-molecule selective inhibitor of BRAF-V600E and BRAF-fusion alterations without inducing paradoxical reactivation of MAPK signaling. **Methods:** This single institution trial of plixorafenib alone (Arm A) or combined with retifanlimab (Arm B) is enrolling patients (18+ years of age) with BRAF-V600E mutant glioma following progression on prior BRAF-targeted therapy who are recommended for a clinically-indicated diagnostic or debulking surgery. Eligible patients have recurrent BRAF-V600E mutant glioma (any grade) with measurable disease (by RANO 2.0), and a Karnofsky performance status ≥ 70 . Leptomeningeal disease is allowed. All enrolled patients will undergo clinically-indicated resection or biopsy for confirmation of disease progression and characterization of putative resistance alterations with a ventricular reservoir placed at time of surgery for CSF sampling. In both arms, patients will initiate oral plixorafenib once clinically recovered from surgery. Patients will take the plixorafenib daily with food. In Arm B, enrolled patients will receive one dose of retifanlimab three weeks prior to surgery, then resume monthly retifanlimab infusions after surgery in combination with oral plixorafenib. MRI, CSF, and plasma assessments will occur approximately every two months to evaluate disease status. The primary trial endpoint is detectable ctDNA at baseline and after one month of treatment with plixorafenib. Secondary endpoints include safety of plixorafenib alone or in combination with retifanlimab, response rate in each arm, and the correlation of ctDNA with disease status over time. The trial is IRB approved and enrollment is ongoing (10 patients per arm). Clinical trial identifier NCT06610682. Clinical trial information: NCT06610682. Research Sponsor: Ivy Brain Tumor Foundation; Fore Biotherapeutics.

Progress report of a phase 2 study of BPM31510 (a lipid nano dispersion of oxidized CoQ10) with vitamin K in combination with standard of care (SOC) RT and TMZ in glioblastoma multiforme (GBM) patients without prior therapy.

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Background: BPM31510 is an investigational, drug-lipid conjugate nanodispersion. Preclinical studies demonstrate that intravenous infusion can achieve plasma concentrations of oxidized CoQ10 approximately 10,000 times higher than baseline physiological levels with its accumulation in organs, including brain. Preclinical studies show that supraphysiological concentrations of CoQ10 induce metabolic shifts in a variety of cancer cells and generate Reactive Oxygen Species (ROS) leading to apoptosis. In Phase 1, the main adverse events were related to mild hepatotoxicity and coagulopathy. All coagulation related issues were alleviated by coadministration of Vitamin K. The Phase 2 trial in newly diagnosed patients with glioblastoma tests whether treatment with BPM31510 results in improved efficacy of standard of care temozolomide (TMZ) and radiotherapy (RT). **Methods:** BPM31510IV-11; NCT04752813 is a single-arm, non-randomized, open-label, phase 2 study of intravenous (IV) BPM31510 + prophylactic subcutaneous (SC) Vitamin K1 with standard chemoradiation and temozolomide (TMZ) in newly diagnosed GBM patients. The primary endpoint is Progression Free Survival at 6 months (PFS6) and 12 months (PFS12) while the secondary endpoints are Overall S (OS) survival and safety. Patients with recent hemorrhage, coagulopathy, or requiring anticoagulants are excluded. SC Vit K and IV BPM31510 are initiated 2-4 weeks after biopsy or tumor resection. After two weeks, standard of care chemoradiation and TMZ are started in combination with weekly IV BPM31510 for 8 weeks, after which IV BPM31510 treatment and standard RT are discontinued with subjects continuing to receive maintenance TMZ treatment for up to 12 cycles as per standard of care. Of the approximately 50 patients enrolled and treated upon the recommendation of an independent safety monitoring committee, 25 will be available for PFS6 efficacy endpoint analysis and these data will be presented. Clinical trial information: NCT04752813. Research Sponsor: BPGbio.

Gliofocus: A global, open-label, randomized phase 3 study comparing niraparib with temozolomide in newly diagnosed MGMT-unmethylated glioblastoma.

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Background: Glioblastoma (GBM) remains a fatal malignancy despite multimodality therapy. Approximately 60% of GBMs lack O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, thus associated with resistance to alkylating chemotherapy and poor survival with median OS of 12.7 months. Poly(ADP-ribose) polymerase (PARP) is a central regulator of DNA damage repair and genomic stability in GBM and represents a rational therapeutic target, particularly in the setting of radiotherapy-induced DNA damage. Niraparib is a selective PARP1/2 inhibitor that has demonstrated excellent central nervous system penetration and favorable tumor pharmacokinetic and pharmacodynamic properties in previously reported early-phase GBM studies. These findings provided the scientific rationale for Gliofocus, a global phase 3 trial designed to evaluate whether replacing temozolomide with niraparib during and after radiotherapy improves outcomes in patients with newly diagnosed, MGMT-unmethylated GBM. **Methods:** Gliofocus is a phase 3, open-label, randomized, two-arm study enrolling total 450 adults with newly diagnosed, MGMT-unmethylated GBM. Eligibility requires histologic diagnosis of GBM per 2021 WHO classification, Karnofsky performance status ≥ 70 , documented MGMT promoter unmethylated status by validated local testing, and no prior GBM-directed therapy other than biopsy or resection. Patients are randomized 1:1 to receive niraparib or temozolomide concurrently with external-beam radiotherapy (60 Gy in 30 fractions using the ESTRO-EANO single-target volume approach), followed by adjuvant monotherapy of niraparib or temozolomide. Treatment continues until centrally reviewed disease progression per RANO 2.0 guidelines or completion of six cycles of temozolomide in the control arm. The primary endpoint is overall survival (HR = 0.698, 88% power). Secondary endpoints include progression-free survival, objective response rate, health-related quality of life, neurocognitive outcomes, and safety. Integrated correlative assessments include centralized imaging review, longitudinal neurocognitive testing, and patient-reported outcomes. Enrollment began in June 2024. The independent data monitoring committee last reviewed the study in January 2026, and recommended continuation as planned. The trial is sponsored by the Ivy Brain Tumor Center with funding/product support from GSK (NCT06388733). GSK was provided the opportunity to provide a courtesy review of the abstract; however, the authors are solely responsible for final content. Gliofocus study is being conducted across a minimum of 80 sites across 12 countries. Clinical trial information: NCT06388733. Research Sponsor: GSK.

Alliance A072301: A phase III trial of radiotherapy followed by adjuvant temozolomide in combination with vorasidenib vs placebo in *IDH*-mutated newly diagnosed grade 3 astrocytoma (VORTEX).

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Background: Treatment for newly diagnosed IDH-mutant astrocytoma, WHO grade 3, is based on the results of the CATNON study, demonstrating benefit of radiotherapy followed by 12 months of adjuvant temozolomide. While temozolomide and radiotherapy significantly improved survival, the prognosis for these patients remains limited and more effective therapies are required. This trial will evaluate the benefit of the addition of the IDH1 and IDH-2 inhibitor vorasidenib to adjuvant temozolomide versus placebo following standard radiotherapy to evaluate possible improvement in outcomes. **Methods:** Alliance A072301 (NCT07215910) is a multicenter, double-blinded phase 3 randomized study to determine if the addition of vorasidenib to adjuvant temozolomide significantly improves progression-free survival (PFS), based on blinded central review in patients with newly diagnosed, IDH-mutant astrocytoma, WHO grade 3. Key inclusion criteria include age ≥ 12 years old, histological confirmation of astrocytoma (absence of 1p/19q codeletion), WHO grade 3, presence of any IDH mutation, plan for radiation and chemotherapy and surgery within 6 months. The presence of CDKN2A/B homozygous deletion, spinal or leptomeningeal disease, as well as prior chemotherapy, cranial irradiation or IDH inhibitor therapy, is exclusionary. 408 patients will be randomized 1:1 to receive vorasidenib 40 mg or placebo daily with 12 cycles of temozolomide following radiotherapy and then continued as monotherapy until disease progression or unacceptable toxicity. Stratification factors include age (< 40 years old vs ≥ 40 years old) and residual disease (< 2 cm vs ≥ 2 cm). Tumor assessments with MRI will be every three months for the first two years, every four months for the next two years and then every six months thereafter as per blinded independent central review using the Response Assessment in Neuro-Oncology (RANO) 2.0 criteria. Key secondary endpoints include PFS by local review, time to next treatment, safety and tolerability, quality of life measures. Exploratory measures will include seizure frequency. The trial will have 85% power to detect a hazard ratio of 0.625 with one-sided type I error rate of 0.025. Enrollment for the trial commenced February 2026. Support: U10CA180821, U10CA180882, U24CA196171. <https://acknowledgments.alliancefound.org>. Research Sponsor: National Cancer Institute; Servier Pharmaceuticals.

A phase 3 randomized trial comparing temozolomide with PCV as adjuvant chemotherapy in grade 2 and 3 diffuse gliomas in adults.

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Background: Both Temozolomide (TMZ) and PCV are standard adjuvant chemotherapy regimens used in treatment of grade 2 gliomas with high risk features and grade 3 gliomas. The PCV regimen has a complex schedule, higher rate of adverse events (esp myelosuppression), and is difficult to administer, but has long-term data with an overall survival benefit. On the other hand, TMZ is an oral drug, with a simple dosing schedule, and fewer adverse events. Currently, there is lack of data directly comparing PCV to TMZ, there is emerging evidence to suggest that PCV may be the regimen of choice for oligodendrogliomas (ODGs). There is often debate on the choice of adjuvant chemotherapy. Hence we are conducting this study to compare TMZ with PCV in this setting. **Methods:** This is an ongoing phase 3, parallel-arm, non-inferiority trial. Adults with high-risk grade 2 (age ≥ 40 years and/or the presence of residual disease ≥ 1 cm after maximal safe resection) or grade 3 gliomas, are randomized 2:1 to receive TMZ or PCV after adjuvant radiation (RT). Patients receive adjuvant focal conformal radiation, with doses between 54 to 59.4 Gy at 1.8-2 Gy/fraction with conventional fractionation. In the TMZ arm, patients receive RT with concurrent TMZ 75 mg/m²/day (max. 49 days) followed by adjuvant TMZ 150-200 mg/m² for 5 of 28 days (max. 12 cycles). In the PCV arm, patients receive Procarbazine 60 mg/m² on days 8-21, CCNU 110 mg/m² on day 1 and Vincristine 1.4 mg/m² on days 8, 29 of a 56-day cycle (maximum 6 cycles). Adjuvant chemotherapy is started within 8 weeks of completing RT. Adverse events are recorded as per CTCAE v4.03. EORTC QLQ C-30 & QLQ BN-20 is used for quality of life (QoL) assessment. Follow up evaluation will be conducted every 3 months in the 1st year, every 4 months in the 2nd year, and every 6 months from the 3rd to 5th year, then annually. The primary endpoint of the study is Progression-Free Survival (PFS). Secondary endpoints are Overall Survival (OS), safety, compliance & QoL. **Sample Size:** Assuming a 3-year PFS of 70% in the PCV arm, with type 1 error of 5% (1- sided), type 2 error of 20%, with 2:1 ratio of accrual (in favor of the TMZ arm) for 10 years, with a study duration of 15 years, to show a non-inferiority by 12% for the upper limit of 95% confidence interval of the PFS with one interim analysis; the sample size estimated by group sequential design for time-to-event outcome was 216. **Statistical analysis:** Kaplan Meir analysis will be used to estimate the PFS & OS and log rank test will be used for comparison between two arms. Cox proportional hazard model will be constructed for calculation of hazard ratio with its 95%CI. An interim analysis will be performed at 82 events of progression. If the log rank p value for the difference in the estimated PFS of the 2 arms is ≤ 0.006 then the trial will be terminated. Otherwise the trial will continue and undergo a final analysis at 163 events of progression. **Clinical trial information:** CTRI/2018/07/015056. **Research Sponsor:** Indian Cooperative Oncology Network (ICON).

BRIDGES: A phase 3 randomized trial of immediate postoperative cesium-131 tile-based radiation therapy followed by abbreviated chemoradiation for newly diagnosed glioblastoma (NCT07195591).

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Background: Glioblastoma remains a lethal primary brain tumor with limited therapeutic progress and a persistent unmet clinical need. Standard management requires maximal safe resection followed by external beam radiation therapy (EBRT) with concurrent temozolomide (TMZ); however, the required 4–6-week postoperative healing interval before initiating EBRT creates a vulnerable window for rapid early progression (REP), defined as radiographic tumor progression occurring between surgery and the start of chemoradiation. REP is detected in more than half of patients and is associated with inferior survival. Tile-based radiation therapy (TBRT) with cesium-131 brachytherapy sources (GammaTile, GT Medical Technologies, Tempe, AZ, USA), offers a strategy to eliminate this treatment gap by immediately initialing localized radiation at the time of resection. A feasibility and safety study (NCT05342883) evaluating TBRT implantation following EBRT has been fully accrued and supports randomized evaluation. The BRIDGES study (NCT07195591) builds on this foundation. **Methods:** NCT07195591 is a prospective, randomized, open-label, multicenter, phase 3 trial to evaluate whether immediate postoperative TBRT followed by abbreviated EBRT with concurrent and adjuvant TMZ improves outcomes compared with standard postoperative EBRT with concurrent and adjuvant TMZ. Eligible adults must have newly diagnosed, radiographic suspicion of glioblastoma, can undergo maximal safe resection, possess a Karnofsky Performance Status score ≥ 70 , and be candidates for standard chemoradiation. Key exclusion criteria include multifocal or disseminated disease, prior cranial radiation or chemotherapy, inability to receive TMZ, and medical comorbidities that would interfere with protocol treatment or follow-up. Patients are randomized 2:1 to receive either TBRT implantation followed by a shortened EBRT course with concurrent and adjuvant TMZ or standard postoperative EBRT with concurrent and adjuvant TMZ. Randomization is stratified by age, sex, prior sub-maximal safe resection, and size of pre-operative tumor. A stratified log-rank test using Kaplan–Meier methods will be done using the stratification factors will be implemented for the primary endpoint. Additional time-to-event endpoints will be analyzed using Kaplan–Meier methods and Cox proportional hazards models, and the analyses will follow the intent-to-treat principle. The trial has two pre-planned interim analyses. A Data and Safety Monitoring Board will oversee the trial and conduct periodic safety reviews. Four of the 766 planned patients have enrolled. Clinical trial information: NCT07195591. Research Sponsor: GT Medical Technologies, Inc.

Prospective, randomized, placebo-controlled phase 2b trial of SurVaxM plus adjuvant temozolomide in newly diagnosed glioblastoma (SURVIVE).

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Background: Survivin is widely expressed in glioblastoma (GBM) and is implicated in tumor cell survival and treatment resistance, supporting survivin-targeted immunotherapy in newly diagnosed disease. The survivin long-peptide conjugate vaccine SVN53-67/M57-KLH (SurVaxM) has shown feasibility, immunogenicity, an acceptable safety profile and promising efficacy, in phase 1 and 2 trials in newly diagnosed GBM. We hypothesize that SurVaxM combined with standard adjuvant temozolomide (TMZ) post chemo radiation will improve outcomes in newly diagnosed GBM and that correlative biomarkers will define patient selection.

Methods: SURVIVE is a prospective, randomized, double-blind, placebo-controlled, multi-center phase 2b trial evaluating SVN53-67/M57-KLH plus standard adjuvant TMZ versus placebo plus standard adjuvant TMZ in adults with newly diagnosed GBM. Patients are randomized 3:2 to investigational vaccine (Arm A) or placebo (Arm B), with stratification by Karnofsky performance status, MGMT promoter methylation status, and IDH status. Study intervention consists of four priming SurVaxM injections administered every 2 weeks followed by maintenance dosing every 8 weeks, administered alongside standard adjuvant TMZ (5 days every 28-day cycle; typically, 6-12 cycles per standard practice). The vaccine regimen is delivered as a survivin peptide conjugate with immunologic adjuvants; blinding is maintained via matched placebo injections. MRI surveillance is performed per protocol to support response assessment and the planned imaging correlatives. Key eligibility criteria include age ≥ 18 years; Karnofsky performance status ≥ 70 ; pathologically confirmed cerebral GBM meeting 2021 WHO criteria with available MGMT and IDH status; gross-total or near-total resection with minimal residual enhancement on immediate postoperative MRI (≤ 72 hours); completion of chemoradiation with $\geq 75\%$ of planned concurrent temozolomide; no evidence of progression on post-chemoradiation MRI; randomization within approximately 16-18 weeks of resection; and dexamethasone ≤ 4 mg/day at enrollment. The planned evaluable sample size is 228 patients (n=137 Arm A; n=91 Arm B). The primary analysis will be conducted in the intention-to-treat population using a two-sided alpha of 0.05, with stratified time-to-event comparisons to account for key baseline factors. The alternate hypothesis assumes a 1-year survival rate of 75% in the SurVaxM group (Arm A; comparable to a median overall survival (mOS) of 29 months assuming an exponential distribution) and 60% in the control group (Arm B; comparable to a mOS of 16 months assuming an exponential distribution). Clinical trial information: NCT05163080. Research Sponsor: None.