Evaluating the diagnostic performance of $^{18}$F-fluciclovine for detection of recurrent brain metastases after radiation therapy: Results from a prospective phase 2 trial.

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**Background:** Differentiating radiation necrosis from tumor progression remains one of the most commonly encountered and clinically challenging scenarios after radiation therapy (RT) for brain metastases (BM). PURSUE (NCT04410367) evaluated the diagnostic performance of $^{18}$F-fluciclovine, an amino acid PET radiopharmaceutical, based on various lesion metrics, to establish image interpretation criteria (IIC) for suspected recurrent BM after RT. **Methods:** Patients with solid tumor BM were enrolled across 7 US sites if they had a previously irradiated ‘reference’ lesion equivocal on MRI for recurrence and were planned for craniotomy. $^{18}$F-Fluciclovine PET (185 MBq) took place <42 days post-MRI and 1-21 days pre-craniotomy. The primary endpoint was the diagnostic performance (sensitivity, specificity, positive-, and negative-predictive value [PPV/NPV]) of different thresholds of lesion $^{18}$F-fluciclovine uptake on qualitative, visual reads vs central histopathological analysis. Lesion $^{18}$F-fluciclovine uptake was assessed qualitatively by 3 independent blinded readers who visually rated the uptake as ‘mild’ (up to blood pool), ‘moderate’ (above blood pool to parotid), or ‘marked’ (above parotid). Secondary endpoints included the diagnostic performance based on different thresholds of quantitative (e.g., lesion SUV) and dynamic measures of uptake. A committee, including 2 expert imaging physicians independent to PURSUE, reviewed all data in round-table meetings to establish the IIC, which were subsequently used to assess diagnostic performance. **Results:** All 23 reference lesions in 23 subjects underwent histopathological analysis, with 10 (43%) confirmed as recurrent tumor. The highest performing qualitative measure was ‘marked’, rendering a sensitivity of 92-100%, with variable specificity of 40-80% across readers. $\text{SUV}_{\text{max}}$ was a reader-independent, high-performing quantitative metric on ROC analysis (AUC 0.87, $\text{SUV}_{\text{max}}$ threshold 4.8 conferring a sensitivity of 80% and specificity of 85%). Dynamic measures did not provide added diagnostic value. After analyzing these metrics, the committee established IIC as: Lesions with $^{18}$F-fluciclovine uptake of a $\text{SUV}_{\text{max}}$ equal to or greater than 4.8, or visually greater than the parotid gland, should be considered suspicious for recurrence. Otherwise, recurrence should be considered unlikely. Application of the IIC resulted in a sensitivity of 80%, specificity of 77-85%, PPV of 73-80%, and NPV of 83-85% across the readers. **Conclusions:** This is the first prospective multicenter trial to evaluate PET characteristics of suspected recurrent BM after RT, verified by histopathology. Qualitative and quantitative IIC show $^{18}$F-fluciclovine to be a high-performing diagnostic tool. These IIC will help evaluate the diagnostic performance of $^{18}$F-fluciclovine PET in future trials. Clinical trial information: NCT04410367. Research Sponsor: Blue Earth Diagnostics.
Background: Elderly patients with glioblastoma have a poor prognosis with phase III trials reporting median overall survival (OS) and global time to deterioration of 6–9 and 1.2 months respectively. 18F-DOPA (3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine) positron emission tomography (PET) is sensitive and specific for identifying regions of high density and biologically aggressive glioblastoma. Proton beam therapy (PBT) can spare more healthy tissue that may improve quality of life for this patient population. With improved targeting of disease along with dosimetric advantages of PBT, this phase II trial tested whether hypofractionated PBT can offer both improved survival and quality of life. Methods: Patients with newly diagnosed glioblastoma aged ≥65 years without contraindications to 18F-DOPA were eligible. Target volumes were defined by PET (tumor/normal brain SUV ≥2.0) and MRI areas of contrast enhancement including surgical cavity. Patients received dose escalated hypofractionated PBT of 35-40 GyE to PET/MRI over 5-10 treatments with 10 mm margin. Patients received concurrent/adjuvant temozolomide. With an alpha of 0.1, 18 of 39 patients would be required to be alive at 12 months for the study to be considered a success. Kaplan-Meier/Cox regression analysis was performed for progression free survival (PFS) and OS. Toxicities were evaluated with CTCAE v4.0. Patients completed EORTC BN20, QLQ-C30, and MMSE questionnaires. Time to deterioration, defined as a 10-point decrease in the score of the function domain or 10-point increase in score of symptom domain, was evaluated. Results: Between 5/2019-6/2021, 43 patients were enrolled, with 4 patients withdrawing due to progression/insurance denial prior to beginning protocol therapy. The median age was 70.2 yrs. and median follow-up was 12.5 months. MGMT methylation was present in 13 (33%). Tumors were multifocal in 10 (26%) and unifocal in 29 (74%). The primary endpoint was met with median PFS/OS was 6.5/12.9 months for all patients and for MGMT methylated patients 11.9/29.8 months respectively. Grade 3 baseline adjusted treatment related adverse events included 1 (3%) confusion, 2 (5%) fatigue, and 1 (3%) seizure. There were no grade 4/5 events. Multivariate analysis revealed MGMT unmethylated, ECOG 2 and biopsy only patients had worse survival. PET volume was more predictive than MRI volume for OS with PET volume>26 cc having a hazard ratio of 3.7. The median time to global deterioration per QLC-C30 was 6.3 months. Conclusions: This phase II trial incorporating 18F-DOPA PET-guided dose escalated hypofractionated proton beam treatment for elderly patients with glioblastoma met its primary endpoint for improved OS and patient reported quality of life compared to historical controls. Further investigation is warranted. Clinical trial information: NCT03778294. Research Sponsor: Marley/Matheson.
PD1 inhibition and GITR agonism in combination with fractionated stereotactic radiotherapy for the treatment of recurrent glioblastoma: A phase 2, multi-arm study.


Background: Despite preclinical evidence that fractionated stereotactic radiotherapy (FSRT) is immunostimulatory, there remains a paucity of data regarding immune effects of FSRT in patients treated with immune checkpoint blockade (ICB). To evaluate the immune impact of FSRT in glioblastoma (GBM), which is refractory to single-agent ICB, and to evaluate the efficacy of the addition of FSRT to ICB for this disease, we conducted a phase 2 trial of the combination of retifanlimab (anti-PD1), INCAGNO1876 (GITR agonist), and FSRT (8 Gy x 3 fractions) in patients with recurrent GBM (rGBM).

Methods: This single-center trial enrolled patients with no prior bevacizumab and dexamethasone dose ≤ 2mg/day. The study included a single-arm, primary efficacy cohort (Cohort A) treated with retifanlimab, INCAGNO1876, and FSRT, and a two-arm neoadjuvant window-of-opportunity cohort (Cohort B) for patients needing tumor resection. In Cohort B, patients on Arm B1 received single doses of retifanlimab/INCAGNO1876 plus FSRT prior to surgical resection, and patients on Arm B2 received single doses of retifanlimab/INCAGNO1876 without FSRT prior to surgical resection. We used flow cytometry on tumor tissue and peripheral blood mononuclear cells and plasma proteomics to explore the immune consequences of neoadjuvant ICB, with vs. without neoadjuvant FSRT. Primary endpoint: ORR in Cohort A (null hypothesis, ORR 5%; alternative hypothesis, ORR 25%; n = 16 for 80% power, α = 0.05). Secondary endpoints: progression-free survival (PFS) and overall survival (OS), separately in Cohorts A, B1, B2. Data cut-off: January 18, 2023. Results: 32 evaluable patients: Cohort A, n = 16; Cohort B, n = 16 (Arm B1, n = 8; Arm B2, n = 8). Median follow-up time: 20 months. Most common grade 3/4 treatment-related adverse events: cerebral edema (34%), fatigue (16%). Efficacy in Cohort A: no objective responses, best response of stable disease in 9/16 patients (56%), median PFS 3.9 months (95% CI 2.1 – 6.2 months), median OS 9.4 months (95% CI 8.2 – 10.6 months). Median PFS and OS were significantly longer in Cohort B1 (neoadjuvant immunotherapy + FSRT) vs. Cohort B2 (neoadjuvant immunotherapy, no FSRT): PFS 11.7 vs. 2.0 months (p = 0.0002), OS 20.1 vs. 9.4 months (p = 0.001). Inflammatory cytokine responses were stronger and more sustained in Cohort B1 vs. Cohort B2, with concomitant increases in proliferative T cell responses.

Conclusions: The combination of retifanlimab, INCAGNO1876, and FSRT did not demonstrate efficacy in patients with rGBM when administered without surgical resection. However, among patients receiving neoadjuvant immunotherapy prior to surgical resection, the addition of neoadjuvant FSRT was associated with a significant survival advantage as well as increased inflammatory and cellular immune responses. Neoadjuvant FSRT + ICB warrants further evaluation in rGBM. Clinical trial information: NCT042225039. Research Sponsor: Incyte; Conquer Cancer Foundation of the American Society of Clinical Oncology.
Anti-telomerase vaccine in patients with newly diagnosed, unmethylated MGMT glioblastoma: A phase II study.

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Background: TERT, a subunit of the telomerase complex, is largely expressed in almost all cancers. Among those cancers, glioblastomas (GBM) harbor the highest incidence of activating mutations within the TERT promoter (over 85% of patients). This high incidence underlies the potential role of TERT in oncogenesis, and points out TERT as a highly relevant tumor target in GBM. UCPvax is a therapeutic vaccine composed of two CD4 helper peptides derived from TERT, combined with the montanide adjuvant. We conducted a phase IIa trial to test the immunogenicity, safety and efficacy of UCPvax in patients with newly diagnosed GBM.

Methods: Key inclusion criteria were: histologically confirmed, non-mutated IDH1 glioblastoma, unmethylated MGMT promoter status, previous treatment with concomitant radiotherapy and temozolomide (TMZ), Karnofsky Performance status (KPS) ≥ 70%, steroids < 10mg/ day equivalent prednisone, and lymphocytes count ≥ 0.8 x 10⁹/L. One month after completion of radiation/TMZ, patients started UCPvax vaccinations on days 1, 8, 15, 29, 36 and 43, then every two months until tumor progression, without additional cure of TMZ. Peripheral blood mononuclear cells were collected before treatment, at 1 and 2 months after treatment and, at each vaccination boost. The primary endpoint was an anti-TERT specific CD4 T-cell response measured ex vivo in peripheral blood using IFN-gamma ELISPOT at 2 months. Secondary endpoints included safety, overall survival (OS) and progression-free survival (PFS). Results: Thirty-one adult patients (median age 60-yr old, median KPS 90%) were included in this study. All patients received at least one vaccination, and vaccinations were given for 4.5 months on average (min 2–max 14). At baseline, only one patient had a pre-existing anti-TERT CD4 T-cell response (3%). After immunizations, de novo induction and/or amplification of an anti-TERT response were found in 29/30 pts (97%). An epitope spread response against other tumor-associated antigens was detected in 12/25 pts (48%). No severe (grade 3–4) toxicity was attributable to the vaccination. All patients developed local skin reactions (≤ grade 2), 16 patients complained of transient asthenia (≤ grade 2), and 13 patients experienced local pain (≤ grade 2). In the intent-to-treat population (n=31), the PFS was 8.9 months (95% CI: 7.6–10.6) and the median OS was 17.9 months (95% CI: 16–23). Two years after diagnosis, 26% of the patients were still alive. OS was significantly improved in the patients developing an epitope spread response vs the others (19.3 vs 15.8 months, respectively, p=0.03). Conclusions: UCPvax is highly immunogenic and provides an interesting OS rate in this population of poor prognosis, unmethylated MGMT GBM patients. These data support further clinical studies of UCPvax in GBM patients. Clinical trial information: NCT04280848. Research Sponsor: PHRC.
**Phase II trial of pembrolizumab in patients with brain metastases.**

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**Background:** Brain metastases are an increasing challenge in oncology due to increasing incidence and limited treatments. Recent studies suggest that brain metastases harbor a tumor microenvironment characterized by immunosuppressive phenotypes, which contribute to treatment resistance. Therefore, a logical therapeutic strategy for brain metastases is to evaluate immune-based strategies that augment T cell cytotoxicity.

**Methods:** This study was designed as an open-label, single-stage, single-arm phase 2 clinical trial evaluating the intracranial efficacy of pembrolizumab, a PD-1 inhibitor, in patients with brain metastases of diverse histologies. The target accrual was 58 patients to achieve at least 52 evaluable patients (i.e., received at least one dose of pembrolizumab). The primary endpoint was intracranial benefit, defined as a best response of complete response, partial response, or stable disease by RANO criteria during treatment. The study design compared a null intracranial benefit rate of 10% against an alternative of 24%. If at least 8 patients among the total of 52 had intracranial benefit, the primary efficacy endpoint would be met and pembrolizumab would be considered worthy of further study in this patient population. This design has a type-I error of 10% and power of 89% (target type-II error of 15%).

**Results:** In the 57 evaluable patients, median age was 53 (range 28-80) and 81% were female. Tumor histologies included breast (n = 35), non-small cell lung cancer (n = 7), melanoma (n = 2), small-cell lung cancer (n = 2), sarcoma (n = 2), ovarian (n = 1), pituitary carcinoma (n = 1), pituitary neuroendocrine tumor (n = 1), esophageal adenocarcinoma (n = 1), prostate (n = 1), renal cell carcinoma (n = 1), neuroendocrine carcinoma (n = 1), unknown primary (n = 1) and sinonasal adenocystic carcinoma (n = 1). For the patients with breast cancer, 16 patients had HER-2 positive disease, 17 patients had hormone receptor-positive disease, and 11 patients had the triple-negative subtype. The study met its primary endpoint and achieved an intracranial benefit rate of 42.1% (90% confidence interval [CI]: 31-54%). In addition, seven patients, who had either breast cancer, melanoma or sarcoma, had durable intracranial anti-tumor activity (> 2 years). The extracranial benefit rate in patients with evaluable extracranial disease based on RECIST 1.1 criteria was 45% (18/40; 90% CI: 31-59%). Median overall survival was 8.0 months (90% CI: 5.5-8.7 months). Grade 4 toxicities at least possibly related to treatment were observed in 2 patients: cerebral edema (n = 2). Thirteen patients discontinued treatment for adverse events.

**Conclusions:** Our study of pembrolizumab met overall primary endpoint for intracranial benefit in patients with brain metastases. These results suggest that PD-1 blockade may serve as the backbone of therapeutic strategies for a select group of patients with brain metastases and warrants further evaluation. Clinical trial information: NCT02886585. Research Sponsor: Merck Sharp & Dohme; Massachusetts General Hospital.
INB-200 phase I study of gene modified autologous gamma-delta (γδ) T cells in patients with newly diagnosed glioblastoma multiforme (GBM) receiving maintenance temozolomide (TMZ).

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Background: MHC unrestricted γδ T cells target NKG2D ligands upregulated on tumor cells. IN8bio’s DeltEx chemotherapy resistant cell therapy (CRCT), is a novel γδ T cell genetically engineered to express MGMT to convey temozolomide (TMZ) resistance and allow combination therapy. NCT04165941, a Phase 1 trial assessing the safety of single and multiple infusions of autologous CRCT cells presents updated safety and efficacy data. Methods: Adult newly diagnosed GBM patients with adequate organ function and KPS ≥70% are enrolled. Cells engineered from apheresis were infused through a Rickham catheter placed during surgery. Cohorts (C) 1, 2 and 3 each receive 1, 3 and 6 doses of cells respectively on day (D) 1 of each 28-day maintenance cycle. Patients receive 1 x 10^7 γδ T cells intratumorally with 150 mg/m^2 of TMZ intravenously on D1 of maintenance with the standard Stupp maintenance regimen on D2-5. Primary endpoint is safety; secondary endpoints include progression free and overall survival. Immunologic and genomic correlative analyses are being conducted. Dose limiting toxicities (DLTs) are defined as treatment related ≥ grade 3 cardiopulmonary or hepatic toxicity, grade 4 toxicity exceeding 72 hours or neurologic deterioration that exceeds 2 weeks. Results: 15 patients (53% male; median age 69 (range: 21-76); 80% IDH-WT, 66.7% MGMT unmethylated) were enrolled with 8 dosed (N=3 in C1, 4 in C2, 1 in C3). No patients experienced DLTs, cytokine release syndrome (CRS), or neurotoxicity (ICANS). The most common adverse events (AEs) were Grade 1/2 events including fever, fatigue, nausea, headache, platelet count decreased, incision site pain attributable to TMZ, radiotherapy or disease. One subject had Grade 3 treatment related AEs of UTI, dehydration, and thrombocytopenia. Three evaluable C1 patients have PFS of 8.3, 11.9, 7.4 months and OS of 15.6, 17.7 and 9.6 months respectively. In C2, four patients have been dosed, with no DLTs in 3 evaluable patients; 2 remain progression free at 18.9 and 14.8 months, while a third died without relapse due to pulmonary embolus at 8.7 months. One C3 patient has completed 5 of 6 planned doses without DLT. Patient recruitment continues with anticipated completion in 2023. Conclusions: Data demonstrates that single, repeat doses of CRCT gamma delta T cells have manageable toxicity with continued encouraging trend in PFS and warrants further assessment. Clinical trial information: NCT04165941. Research Sponsor: IN8bio, Inc.
Belzutifan treatment for von Hippel-Lindau (VHL) disease–associated central nervous system (CNS) hemangioblastomas (HBs) in the phase 2 LITESPARK-004 study.

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Background: Patients (pts) with VHL disease are at risk for developing multiorgan tumors and cysts, including CNS HBs. The first-in-class hypoxia-inducible factor 2α (HIF-2α) inhibitor belzutifan showed clinically meaningful antitumor activity in VHL disease–associated renal cell carcinoma (RCC) and other neoplasms in the ongoing, single-arm, phase 2 LITESPARK-004 study (NCT03401788). We present updated results for the subgroup of pts with CNS HBs.

Methods: Adults with a VHL disease diagnosis based on germline VHL alteration, ≥1 measurable RCC tumor, no RCC tumor >3 cm or other VHL tumor requiring immediate surgical intervention, no evidence of metastatic disease, no prior systemic anticancer treatment, and an ECOG PS score of 0 or 1 received belzutifan 120 mg orally once daily. End points evaluated in pts with CNS HBs included objective response rate (ORR), duration of response (DOR), time to response (TTR), and progression-free survival (PFS) per RECIST v1.1 by an independent review committee; linear growth rate (LGR); and safety. CNS HBs were assessed using 2 methodologies: 1) with measurable (≥1 cm) and/or nonmeasurable disease at baseline and with associated cysts, if present; and 2) with measurable disease at baseline, excluding associated cysts, if present, from the lesion measurement.

Results: Of 61 enrolled pts, 50 (82%) had ≥1 CNS HB evaluable at baseline, and 22 (59%) pts had undergone ≥1 CNS-related surgery within 4 years prior to starting belzutifan treatment. As of the April 1, 2022 data cutoff date, median study follow-up for pts with CNS HBs was 38.0 mo (range, 36.1-46.1). ORR was 44% (n = 22; 95% CI, 30-59; 4 CRs, 18 PRs), and DCR was 90% (n = 45; 95% CI, 78-97). Median TTR was 5.4 mo (range, 2.3-33.1), and median DOR was not reached (NR; range, 3.7+ to 38.7+ mo). Median PFS was NR (95% CI, 38 mo to NR). After initiating belzutifan, median LGR for all evaluable pts was −1.6 mm/year (range, −7.0 to 3.1). Of all pts, 25/50 (50%) had ≥1 measurable CNS HBs, excluding any associated cysts. For these pts, ORR was 76% (95% CI, 55-91; 1 CR, 18 PRs), and DCR was 96% (n = 24; 95% CI, 80-100). Median TTR was 3.1 mo (range, 2.5-27.8), and median DOR was NR (range, 3.7+ to 38.7+ mo). Median PFS was NR (95% CI, 36 mo to NR). After initiating belzutifan, median LGR was −1.1 mm/year (range, −3.9 to −0.1). Of all pts, 1/50 (2%) underwent a CNS-related surgery after starting belzutifan. Two (3%) pts discontinued treatment due to treatment-related adverse events. Conclusions: With more than 3 years of treatment with belzutifan, consistent and durable antitumor activity was observed in pts with CNS HBs, which is consistent with findings in other VHL disease–associated neoplasms. Using different methodologies of assessing tumors, our data demonstrated that belzutifan induced the shrinkage of VHL disease–related CNS HBs with or without the presence of associated cysts. Clinical trial information: NCT03401788. Research Sponsor: Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; The Intramural Research Program of the National Institutes of Health, National Cancer Institute Center for Cancer Research, and a grant (U01 CA236489) from the National Cancer Institute.
Clinical and analytical validation of a targeted gene expression biomarker predicting meningioma outcomes and radiotherapy responses.

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Background: Surgery is the mainstay of treatment for meningioma, the most common primary intracranial tumor, but improvements in meningioma risk stratification are needed and current indications for postoperative radiotherapy are controversial. Here we report multicenter clinical and analytical validation of a gene expression biomarker using 1856 retrospective and prospective meningiomas from 12 institutions across 3 continents. Our results reveal the gene expression biomarker provides additional information for meningioma outcomes compared to other classification systems, including prediction of radiotherapy responses. Methods: Gene expression profiling and regularized Cox regression was performed on a discovery cohort of 173 meningiomas to generate a 34-gene expression biomarker and continuous risk score for local recurrence. The model and thresholds for low, intermediate, and high-risk scores were locked and applied to 3 validation cohorts: a multicenter retrospective clinical validation cohort (N = 6 centers, N = 866 meningiomas, median follow-up 5.2 years), a prospective investigator-blinded clinical validation cohort from RTOG 0539 (N = 103 meningiomas, median follow-up 8.4 years), and an analytical validation set for test/re-test and FFPE/frozen analyses, as well as comparison across different platforms for gene expression quantification (N = 8 centers, N = 1219 meningiomas). Gene expression biomarker performance was compared to 9 contemporary molecular classification systems. Favorable versus unfavorable meningiomas were defined as gene expression low risk with any resection, or gene expression intermediate risk with gross-total resection (favorable), versus gene expression intermediate risk with subtotal resection, or gene expression high risk with any resection (unfavorable). Results: The biomarker outperformed WHO grade (5-year local freedom from recurrence [LFFR] delta-AUC 0.11, 95% CI 0.07-0.17, \( p < 0.001 \)) and all other classification systems for LFFR and OS on multivariate analysis, achieving a negative predictive value for recurrence at 5-years of 91.9%. The biomarker was predictive for LFFR after postoperative radiotherapy, with a hazard ratio of 0.33 for unfavorable primary WHO grade 2 meningiomas (95% CI 0.14-0.76, \( P = 0.009 \)), and 0.54 for unfavorable propensity-matched meningiomas across all WHO grades (95% CI 0.37-0.78, \( p = 0.0001 \)). The biomarker reclassified 39.8% of prospectively collected meningiomas from RTOG 0539, including downstaging 30.5% of patients who received postoperative radiotherapy, and was independently prognostic for overall survival on multivariate analysis. Conclusions: A targeted gene expression biomarker improves discrimination of meningioma outcomes compared to recent classification systems and predicts postoperative radiotherapy responses. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.
Prognostic evaluation of surgical re-resection for recurrent glioblastoma using the novel RANO classification for extent of resection: A report of the RANO resect group.

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Background: The clinical effects of re-resection for recurrent glioblastoma remain controversial, and the role of post-operative tumor volume is unclear since leaving certain tumor volumes deliberately behind cannot be ethically justified. A surgical classification system was previously proposed for stratification based upon residual contrast-enhancing (CE) tumor: RANO class 1 was defined as ‘supramaximal CE resection’ (including non-CE tumor removal), class 2 as ‘maximal CE resection’, class 3 as ‘submaximal CE resection’, and class 4 as ‘biopsy’. We aimed to (I) explore the prognostic role of extent of re-resection using this classification and (II) define clinical factors which consolidate the effects of re-resection. Methods: The RANO resect group retrospectively compiled a global, eight-center cohort of patients with first recurrence from a previously resected glioblastoma. The combined associations of re-resection and clinical factors with outcome were analyzed. Kaplan-Meier survival analysis and log-rank test were applied to calculate survival, and Cox’s proportional hazard regression models to adjust for multiple variables (significance level: \( p \leq 0.05 \)). A propensity score-matched analysis was constructed to mimic a randomized clinical trial comparing the different RANO classes. Results: We encountered 681 patients with first recurrence of IDH-wildtype glioblastoma, including 310 patients who underwent re-resection at first recurrence. The use of re-resection was associated with prolonged survival also when stratifying for molecular and clinical confounders on multivariate analysis including pre-operative tumor volume, MGMT promotor status, and non-surgical therapies (HR: 0.65, CI: 0.5-0.8; \( p = 0.001 \)); and \( \leq 1 \) cm\(^2\) residual CE tumor translated into improved survival compared to non-surgical management. Accordingly, ‘maximal resection’ (class 2) had superior survival compared to ‘submaximal resection’ (class 3) (median OS after recurrence: 12 vs. 9 months; \( p = 0.003 \)). Adjuvant chemotherapy further augmented the beneficial effects of lower residual CE tumor. Conversely, ‘supramaximal resection’ of non-CE tumor (class 1) was not associated with prolonged survival but frequently accompanied by post-operative deficits, hampering further treatment. The prognostic role of residual CE tumor was confirmed in propensity score analyses. Conclusions: Extent of resection for recurrent glioblastoma as quantified by residual CE tumor is highly prognostic and the RANO resect classification may serve to stratify patients accordingly. Chemotherapy may favorably contribute to the prognostic associations of re-resection. When pursuing resection of non-CE tumor, intraoperative mapping strategies to minimize the risk of post-operative deficits are recommended. Research Sponsor: None.
A genomic score to predict local control among patients with brain metastases managed with radiation.

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Background: Clinical predictors of local recurrence following radiation among patients with brain metastases (BrM) provide limited explanatory power. As a result, radiation doses and fractionation schemes are prescribed with a “one-size-fits-all” approach. We sought to develop a DNA-based signature of radiation-based efficacy among patients with BrM, utilizing readily testable genes, to identify subpopulations at greater vs. lesser risk of recurrence. Methods: We retrospectively identified 570 patients with 1,487 distinct BrM managed with whole-brain (WBRT) or stereotactic radiation therapy (SRS/SRT) at a tertiary cancer center (2013-2020) for whom next-generation sequencing panel data (OncoPanel, 239 genes) were available on at least one tumor specimen. Local recurrence was assessed in a manner consistent with Response Assessment in Neuro-Oncology – Brain Metastases guidelines (i.e., radiographic enlargement of >20% in maximal cross-sectional diameter). Enlarging lesions managed with salvage treatment prior to >20% enlargement were considered to have recurred on the date of salvage therapy. Fine/Gray’s competing risks regression was utilized to compare local recurrence on a per-metastasis level among patients with vs. without somatic alterations of likely biological significance across 84 OncoPanel genes with a mutational frequency >0.5%. Genes with a q-value <0.10 were utilized to develop a numeric “Brain-Radiation Prediction Score” (“Brain-RPS”) to quantify local recurrence risk. Results: Genomic alterations of potential biological relevance in 11 (ATM, MYCL, PALB2, FAS, PRDM1, PAX5, CDKN1B, EZH2, NBN, DIS3, MDM4) and two genes (FBXW7 and AURKA) were associated with a decreased or increased risk of local recurrence, respectively (q-value <0.10). Weighted scores corresponding to the strength of association with local failure for each gene were summed to calculate a patient-level RPS. On multivariable Fine/Gray’s competing risks regression, RPS [1.66 (1.44-1.92, p<0.001)], metastasis-associated edema [1.89 (1.38-2.59), p<0.001] and receipt of WBRT without SRS/SRT or neurosurgical resection [2.73 (1.78-4.20), p<0.001] were independent predictors of local failure. Conclusions: We developed a genomic score that can be calculated from an extracranial or intracranial site to quantify local recurrence risk following brain-directed radiation. Prior attempts to develop a biomarker-based radiation response signature have not been BrM-specific and have primarily relied on RNA-based measures of radiosensitivity, limiting their utility in clinical practice. To our knowledge, this represents the first study to systematically correlate DNA-based alterations with radiation-based outcomes among patients with BrM. If validated, Brain-RPS has potential to facilitate clinical trials aimed at genomic personalization of radiation treatment among patients with BrM. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.
External validation and nomogram for risk factors of CNS metastasis in patients with clinically localized melanoma.

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Background: Surveillance for CNS mets is not routinely performed in CLM due to lack of evidence-based guidelines. We previously reported factors associated with CNS mets in CLM in a single institution study (MD Anderson Cancer Center; MDA). However, external validation of predictors is needed to develop evidence-based surveillance strategies. Methods: Demographics, primary tumor characteristics, and clinical events were collected for pts diagnosed with AJCC 8th edition Stage I-II melanoma in 1998-2014 in two institutions: MDA and Melanoma Institute Australia (MIA). Cumulative incidence of CNS mets was determined by competing risks method, including death; pts without CNS mets and alive at last follow-up (FU) were censored. The external validation of the MDA prognostic model was determined by calibration and discrimination using data from MIA. A ratio of observed and predicted outcomes (O/P ratio) was used to summarize calibration. An O/P ratio of 1 indicates perfect calibration, < 1 too high, and > 1 too low. The prediction model’s discriminative ability was obtained by area under operating characteristic curve (AUC), ranging from 0.5 (none) to 1.0 (perfect) discrimination. Nomograms for predicting Cumulative Incidence of CNS mets were produced. Results: MDA and MIA cohorts included 4,332 and 9,610 pts, respectively. Pts and clinical characteristics were similar in the cohorts. Median FU time was longer for MDA than MIA (88.9 vs. 26.3 months). The 2-, 5-, 10-year (yr), and final cumulative incidence of CNS mets were 1.5%, 4.9%, 7.8%, and 11.0% for MDA and 1.4%, 4.7%, 7.9%, and 10.8% for MIA pts, respectively. The initial MDA predictive model considered for validation included gender, primary tumor site, melanoma subtype, Breslow thickness (BT), ulceration, mitotic rate (MR), lymphovascular invasion and perineural invasion. External validation of the predictive model was performed at 2, 5, and 10 yrs. The original model’s validation properties were not ideal with the predicted estimates overestimating the observed values; thus the model was refined. The final reduced model evaluated included primary tumor site, melanoma subtype, BT, and MR. For calibration, O/P ratio (95% CI) for this model was 0.96 (0.75, 1.17) at 2 yrs, 0.97 (0.84, 1.11) at 5 yrs, and 1.03 (0.91, 1.15) at 10 years. The AUCs (95% CI) for 2, 5, and 10 yrs were 0.75 (0.70, 0.81), 0.71 (0.68, 0.75), and 0.69 (0.65, 0.72), respectively. The reduced model had similar AUCs with, but better calibration results than the original model. Nomograms of pts with high- and low-risk of CNS mets will be presented. A risk calculator will be available. Conclusions: A validated nomogram including primary tumor site, melanoma subtype, BT, MR can predict risk of CNS mets in CLM. This nomogram/risk calculator will help stratify CLM pts for CNS mets risk and facilitate development of personalized CNS surveillance strategies. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.
Pretreatment clinical parameters associated with intracranial progression burden following an initial stereotactic radiosurgery course in a multi-institutional brain metastases cohort.

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Background: While brain metastasis (BM) velocity is a valuable prognostic metric at time of intracranial progression (ICP), pre-SRS risk factors for post-SRS high-burden intracranial progression (ICP) remain poorly characterized. We hypothesized that pre-SRS clinical parameters are associated with subsequent high-burden (ICP), defined as either ≥5 (ICP5) or new/progressive ≥11 BMs (ICP11).

Methods: All patients completing an initial SRS course for BMs at two institutions from 1/2015-12/2020 were retrospectively identified. Patients with prior whole brain radiation therapy (WBRT) and/or BM resection were eligible. Demographic and clinical parameters were collected. ICP was defined as any radiographic concern for distant and/or in-field progression per multidisciplinary consensus. Overall survival (OS) and freedom from ICP were estimated via the Kaplan Meier method. Cox models assessed association between parameters and freedom from ICP5 and ICP11. Results: We identified 1383 patients completed SRS, with a median follow up of 8.7 months. Patients were 54.8% female, 45.6% with KPS ≥90, and a median of 63.4 years old. Primary tumor types included non-small cell lung (48.7%), breast (14.7%), and melanoma (8.5%). 46.9% had oligometastatic disease (≤5 metastatic foci: including BMs) at SRS, and 53.4% underwent SRS for >1 BM. 10.3% of patients had undergone prior WBRT and 26.1% surgical resection. 555 patients (40.1%) experienced ICP following SRS, of whom 72.6% had 1-4, 11.5% had 5-10, and 15.9% had ≥11 new/progressive BMs. Among patients with ICP, 6-month freedom from ICP was 35.5% (95% CI: 31.1-40.5%) for those with 1-4 BMs at time of ICP, 29.7% (95% CI: 20.4-43.3%) for 5-10 BMs, and 20.5% (95% CI: 13.5-30.1%) for ≥11 BMs (p = 0.016). Respective 12-month OS rates were 56.8% (95% CI: 52.1-61.9%), 46.0% (95% CI: 35.1-60.1%), and 38.7% (95% CI: 29.4-50.9%; p < 0.001). Neurologic symptoms at time of ICP were observed in 21.1% of patients with 1-4 BMs, 28.1% with 5-10 BMs, and 50.0% with new/progressive ≥11 BMs (p < 0.001). On multivariable analysis, superior freedom from high-burden ICP was associated with the following pre-SRS parameters: oligometastatic burden (ICP5: HR 0.68, 95% CI: 0.47-0.97; ICP11: 0.59; 95% CI: 0.36-0.97), no prior immunotherapy (ICP11: HR 0.57, 95% CI: 0.34-0.51), and a single BM at time of initial SRS (1 vs 2 BM, ICP 5: HR 0.51, 95% CI: 0.31-0.82; ICP11: HR 0.45, 95% CI: 0.24-0.84), while primary tumor type was not associated with ICP5 or ICP11. Conclusions: Pre-SRS parameters including polymetastatic burden, prior receipt of immunotherapy, and >1 BM were associated with post-SRS high-burden ICP. High burden ICP developed earlier following SRS completion and was associated with higher rates of neurologic decline and inferior OS. Research Sponsor: None.
A radiomic-based predictive model of lung adenocarcinoma brain metastases and molecular subtypes.

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Background: Non-small cell lung cancer (NSCLC) comprises the largest portion of brain metastases (BM) from solid cancer with 40% of patients developing BM during the course of their disease. There are currently no reliable prediction tools for identifying patients at risk for BM, especially in the early-stage setting where MRI screening is not performed. Furthermore, in the later stage setting, brain MRI are only performed annually. Therefore, there is a critical need to identify high-risk patients for BM that could benefit from MRI surveillance.

Methods: We identified 162 lung adenocarcinoma (LUAD) patients with (N = 66) or without (N = 96) BM that had treatment-naive CT scans with a segmentable lesion. The tumor, surrounding ground glass opacity and necrosis were segmented via 3D slicer to create a volume of interest for radiomic texture analysis and 400 features were extracted. The Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression feature selection method was used to select the most relevant features and models were built using the machine learning method XGBoost classifier. Training and testing sets with random splitting was used for cross validation. We report the accuracy, sensitivity, specificity, and area under the curve (AUC) for each model.

Results: Among the extracted features that LASSO deemed as most discriminative for development of BM, we identified the most relevant features using XGBoost that predicted BM with 79% accuracy, 83% sensitivity, 72% specificity, and 79% AUC ($p = 0.01$) in the overall population. The addition of ground glass opacity and necrosis to the model did not significantly improve performance. Furthermore, the model distinguished those with metachronous vs synchronous BM with 84% accuracy, 83% sensitivity, 86% specificity, and 83% AUC ($p = 0.04$). Our model held up across molecular subtypes (EGFR and KRAS mutant). Importantly, the model was predictive in early-stage patients with 92% accuracy, 96% sensitivity, 83% specificity, and 95% AUC ($p=0.0005$). Moreover, our model predicted for high vs. low overall survival, and was BM-specific as it was not predictive of other sites of metastases. We further developed a model from the CT features that correctly classified KRAS mutant vs. KRAS wild type LUAD with 77% accuracy, 73% sensitivity, 80% specificity, and 80% AUC ($p=0.002$). Conclusions: Utilizing a radiomics approach, we were able to predict BM from primary lung CT features including in stage I and II disease, predict synchronous vs metachronous BM, and distinguish distinct molecular LUAD subtypes. We are currently validating our BM prediction model in a large independent cohort and developing models to classify targetable LUAD-BM molecular alterations utilizing brain MRI scans. These studies will identify patients that require MRI surveillance in the early-stage setting and more intensive surveillance in the late-stage setting for BM. Research Sponsor: Department of Defense.
Longitudinal single-cell (sc) immune profiling of cerebrospinal fluid (CSF) from melanoma patients (pts) with leptomeningeal disease (LMD) treated with intrathecal (IT) and intravenous (IV) nivolumab (N).

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Background: LMD is associated with an extremely poor prognosis in melanoma pts, who currently have very limited treatment options. Our group previously reported initial safety and efficacy results from the dose escalation portion of a first in human phase I/IB trial using IT and IV N (NCT03025256) in melanoma LMD pts. Here we present longitudinal sc profiling of immune cells in CSF from a subset of pts in this trial to better understand the immune composition of this unique microenvironment and features associated with treatment and outcomes. Methods: 39 CSF samples were collected longitudinally from 5 long survivors (LS; IT N number of doses received 10-92) and 5 rapid progressors (RP; IT N doses 2-9) and profiled by sc RNA sequencing. Raw FASTQ reads were aligned to the GRCh38 human reference genome using Cell Ranger v6.0.0 to generate the count matrix. All samples were aggregated by Seurat v4.3.0 and data integration was performed using Harmony v0.1.0. Cells were filtered by following criteria: (1) >20% mitochondrial content, or (2) express <100 or >2,500-5,000 genes, according to sample specific distribution. Empty droplets and doublets were identified by EmptyDrops function from the R package DropletUtils v1.18.0 and DoubletFinder v2.0.3, respectively. We applied normalization, FindVariableFeatures (n = 2,000), scaling, PCA, UMAP and FindClusters to summarize the integrated samples and determine cell clusters. Cell types were annotated based on (1) canonical marker genes using FindAllMarkers, (2) published gene expression signatures, and (3) reference-based tool using Symphony v.0.1.0 on published data: GSE164378 and GSE158803. Statistical analysis was conducted using the Wilcoxon rank-sum test. Results: A total of 10 patients were included in this pilot analysis. Five pts were LS (2 males; IT dose 5 mg, 1 pt; 10 mg, 2 pts; 20 mg, 2 pts; 2 BRAF mutant; 5 negative CSF cytology at baseline) and 5 pts were RP (3 males; IT dose 5 mg, 1 pt; 20 mg, 2 pts; 50 mg, 2 pts; 4 BRAF mutant; 4 positive CSF cytology at baseline). At baseline [prior to cycle (C)1 of IT N], LS pts had a higher percentage of NK cells (relative to total immune cells; \( P = 0.036 \)) and mucosal-associated invariant T cells (relative to total T cells; \( P = 0.036 \)) than RP pts. Prior to C2, LS had a significantly higher percentage of T cells (relative to all cells; \( P = 0.036 \)). The abundance of immune cells and tumor cells were not different between the two groups at C3, at which point pts have received two doses of IT N and one dose of IV N. Conclusions: Exploratory sc analysis of longitudinal CSF samples of LMD pts suggest that baseline immune features may predict outcomes with IT N. Analysis of additional pts is ongoing to provide further insights. Research Sponsor: Dr. Miriam and Sheldon G. Adelson Medical Research Foundation; U.S. National Institutes of Health; Bristol-Myers Squibb.
Long-term survival with IDH wildtype glioblastoma: First results from the ETERNITY Brain Tumor Funders’ Collaborative Consortium (EORTC 1419).

Background: Median survival with glioblastoma remains in the range of 12 months on population levels. Only few patients survive for more than 5 years. Patient and disease features associated with long-term survival remain poorly defined. Methods: European Organization for Research and Treatment of Cancer (EORTC) 1419 (ETERNITY) is a registry study supported by the Brain Tumor Funders Collaborative in the US and by the EORTC Brain Tumor Group. Patients with glioblastoma surviving at least 5 years from diagnosis were identified at 24 sites in Europe, US, and Australia. In patients with isocitrate dehydrogenase (IDH) wildtype tumors, prognostic factors were analyzed using the Kaplan-Meier method and the Cox proportional hazards model. A population-based reference cohort was obtained from the Cantonal cancer registry Zurich. Results: At the cut-off of July 2020, 280 patients with histologically centrally confirmed glioblastoma (189 IDH wildtype, 80 IDH mutant, 11 not otherwise specified) had been registered. In the IDH wildtype population, median age was 56 years (range 24-78 years), 96 patients (50.8%) were female, 139 patients (74.3%) had tumors with O6-methylguanine DNA methyltransferase (MGMT) promoter methylation. Median overall survival was 9.9 years (95% CI 7.9–11.9). Patients without recurrence experienced longer median survival (not reached) than patients with one or more recurrences (8.92 years) (p<0.001) and had a high rate of MGMT promoter unmethylated tumors. Conclusions: Freedom from progression is a powerful predictor of overall survival in long-term survivors with glioblastoma. Never relapsing patients often have MGMT promoter-unmethylated glioblastoma and may represent a distinct subtype of glioblastoma. Clinical trial information: NCT03770468. Research Sponsor: Brain Tumor Funders’ Collaborative; EORTC Brain Tumor Group.
RANO 2.0: Proposal for an update to the Response Assessment in Neuro-Oncology (RANO) criteria for high- and low-grade gliomas in adults.

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Background: Response Assessment in Neuro-Oncology (RANO) criteria for high-grade and low-grade glioma (HGG and LGG) were developed to improve reliability of response assessment in glioma trials. Several limitations of the original RANO criteria have been reported. Methods: To address limitations of the original RANO criteria, a large cohort of patients with newly diagnosed and recurrent glioblastoma were evaluated comparing RANO-HGG with modified RANO (mRANO) and immunotherapy RANO (iRANO) criteria to inform the following proposed updates (RANO 2.0). Results: Based on the 2021 WHO classification of glioma, we recommend a single common set of criteria for all gliomas regardless of WHO grade and IDH mutational status. These criteria will be used for all trials regardless of the treatment modalities being evaluated. In newly diagnosed glioblastoma, the post-radiotherapy MRI, usually obtained approximately 4 weeks after completion of radiotherapy, rather than the post-surgical MRI as proposed in original RANO criteria, will be used as the baseline for comparison of subsequent scans. Since the incidence of pseudoprogression is high in the first 3 months following radiotherapy, rather than the post-surgical MRI as proposed in original RANO criteria, will be used as the baseline for comparison of subsequent scans. Since the incidence of pseudoprogression is high in the first 3 months following radiotherapy, rather than the post-surgical MRI as proposed in original RANO criteria, will be used as the baseline for comparison of subsequent scans. However, confirmation scans are not mandatory after this period nor for recurrent tumors since these scans do not appear to improve reliability in determining progression. For agents with a high likelihood of producing pseudoprogression such as viral therapies and some other immunotherapies, mandatory confirmation of progression with a repeat MRI is an option. The primary measurement will remain the 2-dimensional maximum cross-sectional area of tumor as the simplest method, but where resources are available, volumetric measurements are an option. For IDH wild-type tumors with contrast enhancement, non-enhancing tumor will no longer be evaluated with the possible exception of patients receiving antiangiogenic therapies. However, in tumors with a significant non-enhancing component, both the contrast enhancing and non-enhancing components will be evaluated as target lesions. Conclusions: We hope that these and other proposed changes by the RANO working group will improve response assessment in glioma clinical trials and help the development of more effective therapy for patients. Research Sponsor: None.
BORTEM-17: A phase IB/II single arm, multicentre study investigating the efficacy of sequential bortezomib and temozolomide in recurrent GBM with unmethylated MGMT promoter—The results of an interim analysis.

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Background: Glioblastoma (GBM) is the most frequent, lethal primary brain tumor in adults. Patients harboring tumors with functional O6 methylguanine DNA methyltransferase (MGMT) DNA enzyme gain limited benefit from temozolomide therapy. As shown in preclinical studies, bortezomib depletes the MGMT enzyme, restoring the tumor’s susceptibility to temozolomide, if administered in a precise schedule when the MGMT enzyme is depleted. We hypothesized that recurrent GBM patients with unmethylated MGMT promoter may obtain clinical benefit from sequential BTZ and TMZ treatment.

Methods: BORTEM-17 is a multicenter, open label, single arm, non-randomized phase IB/II trial to investigate potential survival benefit for recurrent glioblastoma patients administered bortezomib 48hrs prior to temozolomide. Sample size is calculated to 63 patients, of whom 10 included in phase IB. The doses of bortezomib is 1.3mg/m2 intravenously days 1, 4, and 7 during 4-week cycle, and temozolomide 200mg/m2 days 5-7. The control group is a retrospective cohort of 467 patients treated at 2 referral hospitals in Norway from January 2015 to December 2017. For the survival analysis, the patients included in BORTEM-17 (n=44) were compared with MGMT unmethylated control, age matched patients (n=116). The pre-defined interim analysis was performed after inclusion of 15 patients and as more than 2 of 15 patients had clinical benefit, the study was continued. Results: Until January 2023, 44 patients with median age 55 years (range 25-69), 30 males and 14 females were treated. Median KPS was 90 (70-100) and median NANO score 1 (0-7). The interim analysis was performed after inclusion of 15 patients in the phase IB and II and clinical benefit was observed in 5 patients. Two of them had tumor volume reduction and three experienced stable disease. The study proceeded to the next step. No treatment related deaths were observed. The most common adverse effects included hematological toxicity, gastrointestinal symptoms, muscle weakness, lower back pain and fatigue. Patients that progressed during the BORTEM-17 trial and were fit for further therapy received treatment at their physician’s discretion. The preliminary data analysis after 44 of planned 63 patients were treated indicate prolonged median survival for BORTEM-17 patients 19.0 months vs 12.2 months of control MGMT unmethylated age matched patients. Median survival after recruitment is 5.5 months (1.0-23.8). Conclusions: The sequential BTZ+TMZ therapy is safe, feasible and effective as indicated by preliminary data when 70% of planned MGMT unmethylated patients have been included. Preliminary data indicate that the combination of BTZ and TMZ may offer an additional line of treatment with limited toxicity to the group of patients with particularly dismal prognosis. Clinical trial information: NCT03643549. Research Sponsor: Norwegian Cancer Society and KLINBEFORSK Norway.
**EO2401 (E) peptide immunotherapy + nivolumab (N) +/- bevacizumab (B) in recurrent glioblastoma (GB): E0GMB1-18/ROSALIE.**

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**Background:** EO2401 was designed to activate/expand existing memory T cells recognizing specific protein sequences from gut bacteria, which cross-react with tumor associated antigens (TAAs). E contains 3 CD8 HLA-A2 epitopes with mimicry to GB-TAAs (IL13Rα, BIRC5, and FOXM1) and the CD4 epitope UCP2. **Methods:** Patients (pt) at 1st progression GB received E (300 μg/peptide, q2w x4 then q4w) with N (3 mg/kg q2w) in cohorts: 1a E x2 → EN; 2a/1, 2a/2 and 2b EN from start; 2c EN x2 → surgery → EN; 3/1 and 3/2 EN + B (10mg/kg q2w) (Table). **Results:** Among 100 treated pt EN+/−B was well tolerated, with E associated events limited to local skin reactions (45% of pt; 96% Grades 1/2, and 4% Grade 3) and N-/B-tox consistent with historical data. EN induced immune response against all 3 mimics in 94% of 35 tested pt (all pt responded against at least 2 mimics), detectable as early as 2 weeks after first EN, and with durations beyond 10 months. Cross-reactivity against human peptides found in 89%. **Conclusions:** EN+/−B was well tolerated and generated fast and durable immune responses. EN survival like current standards. Delayed N was not advantageous for outcome. sLDB increased trt duration of EN, and improved efficacy. Continuous B plus EN further improved efficacy. Neo/adjuvant EN was clinically feasible. Updated data, including C3/2 to confirm C3/1, to be presented. Clinical trial information: NCT04116658. Research Sponsor: Enterome.

**Table:**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Ongoing treatment (trt) (pt)</th>
<th>Trt durationa</th>
<th>Disease Control Rateb</th>
<th>Duration of disease controlc</th>
<th>Objective response rate (PR+CR)</th>
<th>Progression-free survivald</th>
<th>Survivalc</th>
<th>Follow-up survivalc; pt alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a (n=23)</td>
<td>ENa</td>
<td>0%</td>
<td>1.4 (0.01-23.9)</td>
<td>22%</td>
<td>3.5 (1.8-10.0)</td>
<td>9%</td>
<td>1.6 (0.03-11.2)</td>
<td>22.1</td>
</tr>
<tr>
<td>1a (n=21)y</td>
<td>E =&gt; ENb</td>
<td>0%</td>
<td>2.8 (0.03-24.0)</td>
<td>2%</td>
<td>3.3 (2.7-24.0)</td>
<td>5%</td>
<td>1.8 (0.02-11.2)</td>
<td>10.0</td>
</tr>
<tr>
<td>2a (n=15)</td>
<td>ENc</td>
<td>20%</td>
<td>3.2 (0.5-11.0)</td>
<td>40%</td>
<td>4.1 (5.2-9.5)</td>
<td>13%</td>
<td>3.6 (0.09-9.5)</td>
<td>10.8</td>
</tr>
<tr>
<td>2b (n=10)</td>
<td>ENd</td>
<td>33%</td>
<td>7.9 (2.3-10.9)</td>
<td>83%</td>
<td>9.0 (5.9-9.2)</td>
<td>Na</td>
<td>7.3 (1.9-12.4)</td>
<td>11.5</td>
</tr>
<tr>
<td>2c (n=9)</td>
<td>ENc peri-op</td>
<td>67%</td>
<td>0.5 (0.5-8.5)</td>
<td>40%</td>
<td>0.0 (0.5-8.0)</td>
<td>Na</td>
<td>6.7 (0.4-8.0)</td>
<td>5.6</td>
</tr>
<tr>
<td>3/1 (n=11)</td>
<td>EMB</td>
<td>9%</td>
<td>5.0 (0.5-20.2)</td>
<td>91%</td>
<td>6.0 (3.1-20.2)</td>
<td>55%</td>
<td>6.0 (0.0-20.2)</td>
<td>17.2</td>
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<tr>
<td>3/2 (n=15)</td>
<td>EMBb</td>
<td>73%</td>
<td>3.3 (1.4-4.2)</td>
<td>92%</td>
<td>3.3 (1.7-3.7)</td>
<td>33%</td>
<td>3.0 (0.0-3.7)</td>
<td>9.5</td>
</tr>
</tbody>
</table>

NA not applicable; NR not reached.

a Measurable disease: >3 pt in safety lead-in; b Option for symptom driven, time-limited, low-dose B (sLDB): 5 mg/kg q2w, median of 3 doses to 1a=10 pt (56%); NA for 3 pt safety lead-in. 2a/5-5 pt (33%); 2b=1 pt (33%); NA for 3 initial pt; 2c=3 pt (33%); EN in 1 pt as individual use after 24 mo study period. c Non-measurable disease, adjuvant post-surgery in 4 of 6 pt; d PR with stable disease (SD), partial- or complete response (PR/CRI) per RECIST, reflex (range) in months per Kaplan-Meier; e DCR in n=8 (1 pt early), ORR NA, only 2x E admin pre-surgery; f DCR and ORR in n=12 (3 pt early), ORR also unconfirmed.
Immune profiling in patients with glioblastoma treated with VT1021 in a phase I/II expansion study.

Jian Jennifer Chen, Melanie Vincent, David M. Peereboom, Randolph Watnick, Susanne Fyfe, Wendy Li, Suming Wang, James Mahoney, Michael Cieslewicz, Jing Watnick; Vigeo Therapeutics, Inc., Cambridge, MA; Vigeo Therapeutics, Cambridge, MA; Cleveland Clinic, Cleveland, OH; Boston Children’s Hospital, Boston, MA; Vigeo Therapeutics INC, Cambridge, MA

Background: The cyclic peptide VT1021 is a first-in-class therapeutic agent that has been shown to inhibit tumor growth via stimulation of thrombospondin-1 (TSP-1) and reprogramming the immune tumor microenvironment (TME) in preclinical models. Subsequently, VT1021 has been tested in a phase I/II clinical study in solid tumors (NCT03364400) and has advanced to a phase II/III clinical study in glioblastoma (NCT03970447). VT1021 has demonstrated promising single-agent clinical activity against recurrent glioblastoma (rGBM) in a phase I/II expansion study. Among 22 evaluable subjects with rGBM, 3 had complete response (CR), 1 had partial response (PR), and 6 had stable disease (SD) with an average study duration of over 120 days. One subject has been on VT1021 treatment for > 900 days with no measurable lesion left. The overall disease control rate (DCR) was 45%. Here, we sought to examine the peripheral immune cell profile(s) in response to VT1021 and explore the association between these profiles and clinical responses in rGBM subjects. Methods: In the phase I/II expansion study, 22 evaluable rGBM subjects received VT1021 at a dose of 11.8 mg/kg (twice per week intravenously) until disease progression. Peripheral blood samples were collected from all evaluable subjects; immune cell profiles were analyzed by flow cytometry. Results: The immune profiles following VT1021 treatment on day 1 did not vary significantly among rGBM subjects, regardless of response. Intriguingly, after long-term VT1021 treatment (day 53), our analysis of the immune profiles revealed beneficial and sustained changes in three cytotoxic T Cell (CTL) parameters and PD-L1+ MDSCs that correlated with response. Specifically, CR/PR subjects showed a 20% increase in total CTLs (Pre 33.79% vs. 6hr 40.42%), a 66% increase in proliferating CTLs (Pre 1.37% vs. 6hr 2.28%) and a 63% increase in CTL/Treg ratio (Pre 7.85 vs. 6hr 12.81) on day 53 of VT1021 treatment. In contrast, SD and PD subjects exhibited no change or decrease in these three CTL parameters, respectively. We also observed that CR/PR subjects experienced a sustained decrease in PD-L1+ MDSCs after VT1021 treatment (day 1 Pre 95.96% vs. day 53 Pre 92.66% and day 53 6hr 88.06%). Conversely, the sustained decrease of PD-L1+ MDSCs after VT1021 treatment was not observed in SD and PD subjects. Conclusions: Here we report that the durable responses of peripheral immune cells to VT1021 may be associated with better clinical outcomes in rGBM subjects. These findings are consistent with the MOA of TSP-1 to reprogram the TME by stimulating immune and inflammatory cell functions. While the interpretation of our data is limited by the lack of a control arm and the small sample size, the results provide a signal and warrant continued analysis of these parameters in the ongoing phase II/III trial. Research Sponsor: Vigeo therapeutics.
Ombipemut dosing emulsion (ODE) + bevacizumab (bev) vs bev alone in patients (pts) with recurrent or progressive glioblastoma (rGBM).

Samuel Aaron Goldlust, Jong Hee Chang, Yoshitaka Narita, Mary Roberta Welch, Richard M. Green, Jan Drappatz, David Eric Piccioni, Yu Jung Kim, Jason M. Melear, Shota Tanaka, Kuo-Chen Wei, Karen L. Fink, Marshall W. Pitz, Timothy Francis Cloughesy, John Frederick de Groot, Nanci McClellan, Matthew Hitron, Bo Xu, Bo Jin, Claudia Lebedinsky; John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; Severance Hospital, Seoul, South Korea; Department of Neurosurgery and Neuro-Oncology, National Cancer Center Research Institute, Tokyo, Japan; Columbia University Medical Center, New York, NY; Kaiser Foundation Hospital - Los Angeles, Los Angeles, CA; University of Pittsburgh Cancer Institute, Pittsburgh, PA; UC San Diego Moores Cancer Center, La Jolla, CA; Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; Texas Oncology PA, Austin, TX; The University of Tokyo Hospital, Bunkyo-Ku, Japan; New Taipei Municipal Tucheng Hospital, Taoyuan City, Taiwan; Baylor Scott and White Health, Dallas, TX; CancerCare Manitoba, Winnipeg, MB, Canada; Ronald Reagan UCLA Medical Center, Los Angeles, CA; University of California, San Francisco, San Francisco, CA; Sumitomo Pharma Oncology, Marlborough, MA; 84 Waterford Drive, Marlborough, MA

Background: ODE is an investigational cancer vaccine derived from Wilms tumor 1. WIZARD was a randomized, adaptive, phase 3 study to test ODE + bev vs bev in rGBM pts (NCT03149003). Patients were stratified prior to randomization based upon KPS [60 or 70] vs [80 to 100] and extent of resection at initial diagnosis. Patients with low KPS (e.g., 60) are generally underrepresented in clinical trials.

Methods: Pts ≥18 years with GBM at first recurrence were enrolled. Overall survival (OS) was the primary endpoint; the key secondary endpoint was the 12-month OS rate. The primary and the key secondary endpoints were tested using 1-sided test with an overall significance level 2.5%. The Lan-DeMets error spending function based upon O'Brien-Fleming stopping boundaries was used to adjust the significance level for the interim and final analyses. Results: From April 2018 to Aug 2021, 217 pts were randomized 1:1; 109 to ODE + bev and 108 to bev. OS was analyzed after 185 events with a median follow-up of 31.8 months (mo). Pts at baseline had a median age of 60 years, 45.2% reported corticosteroid use, 29% had KPS 60 or 70, 7.8% had tumors that harbored IDH1 or 2 mutations, and the median tumor volume was 10,532 mm³. Baseline characteristics between treatment arms were balanced in the ITT and KPS subgroups. Pts with KPS 60 or 70 had more corticosteroid use, worse NANO scores, and larger tumor burden than those with KPS 80-100. The study did not meet its primary endpoint of OS by ITT (ODE + bev: 10.2 mo vs bev: 9.4 mo, 1-sided p-value: 0.2159). Pts with KPS 60 or 70 had longer OS when treated with ODE + bev (8.2 vs 6.3 mo, 45% death risk reduction, 1-side p value: 0.0119). Grade 1 or 2 injection site reaction was the most common TEAE in the ODE + bev arm. No clinically significant difference in safety was noted between KPS subgroups.

Conclusions: The data in pts with KPS 60 or 70 suggested benefit with ODE + bev that was consistent across different endpoints and that warrants further validation. Clinical trial information: NCT03149003. Research Sponsor: Sumitomo Pharma Oncology.

Efficacy outcomes by KPS subgroup (ITT population).

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>KPS 60 or 70</th>
<th>KPS 80-100</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ODE + bev</td>
<td>Bev</td>
</tr>
<tr>
<td></td>
<td>(N = 32)</td>
<td>(N = 31)</td>
</tr>
<tr>
<td></td>
<td>(N = 77)</td>
<td>(N = 77)</td>
</tr>
<tr>
<td>mOS (mo), 95% CI</td>
<td>8.2 (4.3,10.5)</td>
<td>6.3 (4.1,7.4)</td>
</tr>
<tr>
<td>12 mo OS rate (%)</td>
<td>29.5 (22.9)</td>
<td>12.9 (11.6)</td>
</tr>
<tr>
<td>mOS excluding IDH1 or 2, 95% CI</td>
<td>8.2 (5.8,11.0)</td>
<td>6.3 (4.1,7.4)</td>
</tr>
<tr>
<td>mPFS (mo), 95% CI</td>
<td>4.8 (3.5,8.1)</td>
<td>2.9 (1.9,3.7)</td>
</tr>
<tr>
<td>ORR % (n/N)</td>
<td>21.9 (7/32)</td>
<td>12.9 (4/33)</td>
</tr>
<tr>
<td>DCR % (n/N)</td>
<td>78.1 (25/32)</td>
<td>45.2 (14/31)</td>
</tr>
<tr>
<td>Without neurologi-</td>
<td>56</td>
<td>28</td>
</tr>
<tr>
<td>cal progression at 6 mo (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Progression free survival: PFS; overall response rate: ORR; disease control rate: DCR using mRANO by central review.

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A randomised phase II multicentre study of ipilimumab with temozolomide vs temozolomide alone after surgery and chemoradiotherapy in patients with recently diagnosed glioblastoma: Ipi-Glio.

Paul James Mulholland, Nicholas Fraser Brown, Catherine McBain, Lucy Brazil, Sharon Peoples, Sarah Jefferies, Fiona Harris, Puneet Plaha, Anup Vinayan, Claire Brooks, Samia Hussain, Susan J. Dutton, Stasya Ng, Stephanie Levy, Timothy Coutts; University College Hospital-London, London, United Kingdom; The Christie Hospital, Manchester, United Kingdom; Guy’s Hospital, Cancer Centre, London, United Kingdom; Western General Hospital, Edinburgh, United Kingdom; Addenbrooke’s Hospital, Cambridge, United Kingdom; Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; Oxford University Hospitals, Oxford, United Kingdom; Mount Vernon Cancer Center, Northwood, Middlesex, United Kingdom; University of Oxford, Oxford, United Kingdom; The University of Oxford, Oxford, United Kingdom

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the Journal of Clinical Oncology.

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**Background:** TTFields induce anti-tumor immunity via simultaneous activation of type-1 interferon (T1IFN) pathways of the STING and AIM2 inflammasomes and immunogenic cell death. Thus, TTFields-treated GBM cells may provide a complete in situ vaccination platform and synergize with immune checkpoint inhibitors to prolong survival in GBM patients. **Methods:** We enrolled 26 newly diagnosed GBM patients in a pilot phase 2 study combining TTFields, pembrolizumab and maintenance temozolomide (TMZ). To distinguish immune effects of TTFields from those of pembrolizumab, TTFields was started at cycle 1 of TMZ while pembrolizumab (200 mg IV every 3 weeks) at cycle 2 of TMZ. Primary endpoints were progression-free survival (PFS) versus case-matched controls treated with TTFields plus TMZ only in the EF-14 study. Secondary endpoints included overall survival (OS), toxicity, and signature and mechanism of response by multiomics analyses of PBMCs and tumors. **Results:** The median age was 60.5 years. Fourteen (54%) had biopsy only or partial resection. Nineteen (73%) had unmethylated MGMT and 3 (11.5%) had an IDH mutation. Median PFS was 12.0 months versus 5.8 months in a case-matched control cohort of 26 patients (HR = 0.466; 95% CI: 0.234-0.936; Log Rank \( P = 0.007 \)). Twelve-month PFS was 50.0% versus 28.2% in controls; \( P = 0.058 \). Median OS was 24.8 months versus 14.7 months in controls (HR = 0.388; 95% CI: 0.194-0.775; \( P = 0.039 \)). Two-year OS was 52.4% versus 12.0% in controls; \( P = 0.004 \). Six of 15 (40%) patients with measurable disease achieved partial to complete response. In a Cox regression analysis adjusting for key prognostic factors, \( P \)-value reached 0.0317 for PFS and 0.0074 for OS. The most common serious adverse events were thromboses, seizures, and metabolic disturbances in 4 (15%), 3 (11.5%), and 2 (7.7%) patients, respectively. Molecular analyses prior to the addition of pembrolizumab confirmed robust T cell activation by TTFields via the T1IFN trajectory, as evidenced by a high correlation between TCRab clonal expansion and T1IFN responsive plasmacytoid dendritic cells (Spearman coefficient = -0.8; \( P = 0.014 \)) and defined a T cell-based gene signature of TTFields effects. Subsequently, the ability of the top expanded TCRab clones to adapt to the everchanging tumor microenvironment through successful clonal switching by 2 months after the addition of pembrolizumab strongly predicted response to the triple combination in a Cox HR fit model for OS with a concordance rate of 0.876, Log Rank \( P = 0.031 \). **Conclusions:** The triple combination was well tolerated and demonstrated promising efficacy in newly diagnosed GBM. Multiomics analyses confirmed the robust in situ immunizing property of TTFields with synergy with pembrolizumab and identified potential signatures of response to TTFields and the triple combination. Correlative analysis will be updated. Clinical trial information: NCT03405792. Research Sponsor: Novocure.
Short-length DNA fragments in plasma to predict clinical outcome in unresected glioblastoma patients.

Maxime Fontanilles, Arthur Daban, Ludivine Beaussire, Émilie Léveque, Isabelle Tennevet, Olivier Langlois, Ovidiu Veresezan, Florent Marguet, Florian Clatot, Frédéric Di Fiore, Nasrin Vasseur; INSERM UMR 1245 Brain And Cancer Genomics, Rouen, France; Cancer Centre Henri Becquerel, Rouen, France; Institute of Research Onco-Normand (IRON), Rouen University Hospital and Centre Henri Becquerel, Rouen, France; Rouen University Hospital Charles Nicolle, Rouen, France; Institute of Research Onco-Normand (IRON), Rouen University Hospital and Centre, Rouen, France; Digestive Oncology Unit, IRON group, Rouen Hospital, University of Normandy, Rouen, France; INSERM UMR 1245, IRON Group, University of Normandy, Rouen, France

Background: Early prediction of therapeutic response is an important issue in glioblastoma patients. Cell-free DNA (cfDNA) concentration in plasma shown potential prognostic value. cfDNA release is influenced by non-tumor parameters. Short-length cfDNA (slDNA) may better reflect tumor evolution. The aim was to investigate plasmatic slDNA as prognostic marker in unresected glioblastoma patients.

Methods: An ancillary study of a prospective trial was conducted (GLIOPLAK trial). Patients had newly diagnosed and histomolecular confirmed glioblastoma IDH wild-type (WHO 2021 classification). Patients with resected tumor were excluded. All patients underwent radiotherapy/temozolomide (RT/TMZ) schedule after biopsy. Plasmas were collected at three times during first-line treatment: before (pre-), after (post-) RT and at the time of disease progression/relapse. Cell-free DNA (cfDNA) was extracted from plasma using the QIAamp circulating nucleic acid kit (Qiagen). Short-length DNA (slDNA) fragments (equal or lower than 250 bp length) concentration was calculated based on AUC after automated electrophoresis using 4200 TapeStation System. Primary objective was to investigate the impact on survival of slDNA during RT/TMZ phase. Secondary objectives were to explore the association between tumor volume, corticosteroid exposition and slDNA. Results: Thirty-eight patients were included: median age was 63 [interquartile range 55-66], 84.2% (n=32) had Karnofsky index higher than 80% at baseline and median overall survival (OS) was 13.3 months [CI 95% 11.5; 15.5]. slDNA was detected in 69.4% at the pre-RT time (mean 722.3 pg/ml ±sd 1257.7) and in 83.3% at the post-RT-time (686.1 pg/ml ±1217.1). One third of the patients experienced a slDNA decrease between pre- and post-RT time. Presence of slDNA at the pre-RT time was associated with improved OS: median of 11.7 months [9.8-19.6] in the slDNA(+) group (n=25) versus 8.8months [5.5-NA] in the slDNA(-) group (n=11), HR 0.309 [0.133-0.716], log rank p=0.004. Decrease of slDNA concentration was also associated with better outcome compared to stability or increase of slDNA between pre- and post-RT: respectively median OS 14.1 vs 10.1 months, 0.424 [0.197-0.909], p=0.02. Corticosteroid exposition and dose were not correlated to slDNA concentration at pre-RT or slDNA variation (respectively correlation coefficient 0.081 and 0.047). At pre-RT, presence of slDNA was independent of tumor volume: mean 265.0 cm3 ±84.7 in slDNA(+) group vs 237.7 cm3 ±115.7 in slDNA(-) group, p=0.492. Total circulating cfDNA concentration did not influence OS in our cohort. Conclusions: slDNA during the RT/TMZ phase is an independent prognostic marker in unresected glioblastoma patients. The role of slDNA as a biomarker for adaptive treatment after RT as well as non-invasive molecular characterization tool can be explored in dedicated trial. Clinical trial information: NCT02617745. Research Sponsor: Cancer Centre Henri Becquerel; Association de Rechercher Contre les Tumeurs Cérébrales (ARTC).
Association of CDK4 amplification with duration of response to bevacizumab in glioblastoma.

John L. Villano, Rachael M Morgan, Shulin Zhang, Jill Kolesar, Joanne Xiu, Hilary Seifert, Theodore Nicolaides, Stephanie Rock, Santosh Kesari, Sonikpreet Aulakh, Eric T. Wong, Michael J. Glantz; University of Kentucky, Lexington, KY; University of Kentucky Chandler Medical Center, Lexington, KY; University of Kentucky, Department of Pharmacology, Lexington, KY; Caris Life Sciences, Phoenix, AZ; Caris Life Sciences, Irving, TX; CARIS Life Sciences, Irving, TX; Saint John’s Cancer Institute at Providence Saint John’s Health Center, Santa Monica, CA; West Virginia University, Morgantown, WV; Rhode Island Hospital, Providence, RI; Penn State Milton S. Hershey Medical Center, Hershey, PA

Background: Bevacizumab remains the standard second line therapy in glioblastoma (GBM) with reported improved progression free survival, but not overall survival. We investigated a large clinicogenomic database of GBM patients treated with bevacizumab for molecular alterations associated with treatment outcome. Methods: Molecular profiles of GBM were tested by next-generation sequencing (NGS) of DNA (592 genes, NextSeq or whole-exome sequencing, NovaSeq) and RNA (whole transcriptome sequencing, NovaSeq) at Caris Life Sciences (Phoenix, AZ). Gene amplification was determined by NGS with a threshold of ≥ 6 copies. Real-world survival information was obtained from insurance claims data. Time-on-treatment (TOT) of bevacizumab was calculated from start to finish of treatment while post-bevacizumab overall survival (bevOS) from start of bevacizumab to last day of contact. Short-term (ST) and long-term (LT) responders were defined as those with TOT ≤ 6 months and ≥ 1 year, respectively. Kaplan-Meier estimates were calculated and significance was determined as p values of < 0.05. For molecular comparisons, Fisher’s exact tests and Mann-Whitney U were used when appropriate. Results: Among the total of 383 ST and 107 LT patients identified, no significant difference in gender or age were seen. The LT cohort had significantly longer bevOS compared to the ST cohort (HR 0.27, [95% CI: 0.28-0.35], p < 0.0001). Interestingly, CDK4 amplification was seen in 23% (18/78) of LT patients but only 7% (21/300, p = 0.0002) of ST. When investigating the total cohort of 498 GBM treated with bevacizumab, CDK4 amplified patients demonstrated significantly improved TOT compared to non-amplified (HR: 0.639, [0.48-0.85], p = 0.002). Conversely, the ST cohort had significantly more EGFR amplifications than the LT cohort (43%, 130/300 vs. 19%, 15/79, p < 0.0001). In the total bevacizumab-treated cohort, EGFR-amplified GBM had significantly worse TOT on bevacizumab than non-EGFR amplified GBM (HR 1.387, [1.15-1.67], p < 0.001). No associations were seen in other alterations explored including PIK3CA mutation (HR = 0.81 [0.587-1.113], p = 0.2), EGFR mutation (HR: 1.209, [0.977-1.495], p = 0.1) or RAF1 (HR: 0.647, [0.318-1.317], p = 0.2). Conclusions: Using a large clinical genomic database with GBM subjected to comprehensive molecular profiling, we demonstrated that amplification of CDK4 and EGFR were associated with long-term and short-term responses to bevacizumab, respectively. This warrants further investigation in independent cohorts controlled for age and other prognostic factors. If confirmed, a genetic basis for treatment optimization may provide meaningful clinical outcomes. Research Sponsor: University of Kentucky; CARIS.
ctDNA detection in patients with brain metastases arising from solid tumors.

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Background: While circulating tumor DNA (ctDNA) is a routine tool for therapeutics in metastatic solid tumors, data in those with stable and active brain metastases (BrMs) is limited. We assessed genomic alterations in ctDNA from patients (pts) with solid tumor BrMs in three groups: isolated BrMs/stable extracranial disease (iCNS), concurrent brain and extracranial progression (cCNS), and extracranial progression with no active BrMs at ctDNA draw (eCNS). We also compared ctDNA alterations between pts with and without BrMs. Methods: Pts with BrMs and a Guardant 360 profile (n=253) from the Duke Molecular Registry of Tumors between 01/2014 – 12/2020 were identified. Intracranial and extracranial disease status were determined via investigator assessment (RECIST and RANO-BM criteria) within 30 days of ctDNA test. Mutant allele fraction (MAF) was defined as the % of mutant alleles divided by total alleles at a given loci. Differences in mean ranks of the MAF % maximum were compared using the Kruskal-Wallis test and pairwise comparisons with the Dwass, Steel, Critchlow-Fligner multiple comparisons post-hoc procedure. We compared differences in MAF >1% using the chi-square test. Results: Among the 253 pts with BrMs: 29 (12%) had iCNS, 160 (63%) cCNS, and 64 (25%) eCNS. The two most common tumor types were breast (BC, 12.0%) and non-small cell lung cancer (NSCLC, 76.4%). Median MAF was lower in the iCNS group (1.6%) vs cCNS (4.8%) p=0.002, but eCNS did not differ (2.6%). In pts with BC BrMs, ESR1 mutations were most frequent in the iCNS group (67%), followed cCNS (54%) then eCNS (18%) (p = 0.09) as were PIK3CA mutations, iCNS(50%), cCNS (46%), and eCNS (27%), p = 0.55. In pts with NSCLC BrMs, EGFR mutations were most frequent in the iCNS followed by cCNS then eCNS (67%, 40% and 37%, p = 0.08). KRAS mutations were more frequent in cCNS followed by eCNS and iCNS (30%, 17% and 6% p = 0.031). Patients with no BrMs (n=449) included 24% breast and 76% NSCLC. In the ctDNA, ESR1 and BRCA2 mutations were more frequent in pts with BC BrMs than those without (60% vs 25%, p< 0.001) and (17% vs 5%, p=0.022), respectively. Mutations in EGFR were more frequent in pts with BrMs vs without (36% vs 17%, p <0.001). Sequencing from both BrMs tissue and ctDNA were available for 8 pts (4cCNS and 4 iCNS). 7 of these (87.5%) had identical mutations in tumor and ctDNA. Conclusions: This study illustrates the feasibility of detecting actionable mutations from ctDNA among pts with BrMs, with and without extracranial disease. A higher frequency of actionable mutations in several targetable genes was observed in ctDNA when comparing pts with and without BrMs, thus providing therapeutic opportunities. Additional studies comparing ctDNA and alterations in BrMs tissue are needed to determine if ctDNA can be considered a surrogate to support treatment decisions. Research Sponsor: None.
Evaluating the diagnostic performance of leptomeningeal diagnosis with CNSide compared to standard cytology.

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Background: Prior reports cited detection rates of leptomeningeal metastases (LM) using CNSide vs standard CSF cytology of 78% vs 55% in NSCLC and 84% vs 52% in various solid tumor cohorts. The objective of this study was to compare the real-world performance of the CNSide assay in diagnosing LM versus CSF cytology from lumbar puncture (LP) and established EANO-ESMD LM diagnostic criteria (EANO). Methods: We retrospectively analyzed all neuro-oncology patients from January, 2020 to December, 2022 with suspected LM who underwent LP with CSF cytology and CNSide. The CNSide assay included tumor cells (CSF-TCs) and cell-free DNA (cfDNA). LM diagnostic probability was defined by EANO criteria. Descriptive statistics and confusion matrix were calculated.

Results: 87 patients (66 [76%] women) met eligibility criteria for inclusion with median age of 63 (23-87) years; 35 (40%) had uncontrolled systemic disease. The most common primary histologies were breast (45%) and lung (41%); 33% of primary lung cancers harbored molecular alterations, while primary breast cancers expressed hormone receptors in 69% and HER2 alterations in 10%. Across all primary histologies, 53 (61%) cases harbored molecular alterations, of which 27 (31%) had molecular alterations also detected by CNSide. For 7 (8%) cases with negative cytology and CNSide, CNSide detected alterations by cfDNA assays. LM was diagnosed by CSF cytology in 23 (27%) cases, consistent with confirmed LM by EANO. 36 (41%) cases had confirmed LM by CSF cytology or CNSide; all cytology positive and equivocal cases were detected by CNSide. Patients with negative CSF cytology were further defined as probable (19, 23%), possible (35, 42%), or (7, 8%) lack of evidence by EANO. Modifying EANO criteria to include both standard CSF cytology and CNSide led to 36 (41%) confirmed LM cases, an increase of 13 cases in addition to the 23 cytology positive cases (+56.5%). Compared to CNSide, standard CSF cytology had a sensitivity of 70%, but an expected 100% specificity. Compared to the established higher specificity of CNSide, EANO had 100% sensitivity, but only 18% specificity for diagnosing LM, assuming all EANO possible, probable, or confirmed cases were positive, while specificity improved to 74% with slight decrease sensitivity to 94% if only probable or confirmed cases were considered positive. Conclusions: In the largest, retrospective, single institution, real-world study, implementation of CNSide showed increased sensitivity relative to standard cytology and increased specificity relative to EANO criteria, and provided clinically relevant, cell-based molecular and cell-free DNA analyses. CNSide increased the diagnostic yield by 56.5%. Research Sponsor: None.
Leptomeningeal carcinomatosis and brain metastases in gastroesophageal carcinoma: A real-world analysis of outcomes, clinical and pathologic characteristics.

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Background: Brain metastasis (BM) and Leptomeningeal Carcinomatosis (LC) are uncommon complications in gastroesophageal carcinoma (GEC) patients (pts). These patients have a poor prognosis and are challenging to study. We described the clinicopathologic features and outcomes in the largest real-world cohort of CNS metastasis in GEC pts. Methods: We conducted a single-center retrospective study of GEC pts treated at the Princess Margaret Cancer Centre from 2007 to 2021 who developed BM. Clinicopathologic characteristics and treatment modalities were reviewed. Survival was calculated from the date of BM or LC diagnosis until date of death/last follow-up using the Kaplan-Meier method. A multivariable Cox proportional hazards regression model was used to examine the association of baseline covariates and survival. Results: Of 3283 consecutive pts with GEC, 101 (3.08%) were diagnosed with BM and 20 with LC (0.61%). Most pts with BM were male (75.3%), non-Asian (93%), with a primary gastroesophageal junction tumor (47%) and adenocarcinoma histology (86%). Among pts with known HER2 status (N= 48), 60% were HER2 positive (defined as IHC 3+ or IHC 2+/FISH+). All patients with LC had adenocarcinoma histology; most were signet-ring subtype (85%), poorly differentiated (80%) histology and only 15% (2/13) were HER2 positive. Median survival was 0.8; 3.8; and 7.7 months (mo) in BM pts treated with palliative care only, radiation only and surgery followed by radiation, respectively (p < 0.001). In LC, median survival was 0.7 mo in pts who had palliative care only (7/20) and 2.7 mo for those (13/20) who had whole brain radiation therapy (WBRT) (p < 0.008). Multivariate analysis showed a higher probability of death in patients with number of BM ≥4 (p = 0.02) and predicted superior survival in patients who received radiation and surgery followed by radiation (p = 0.02). Conclusions: This is the most comprehensive summary of clinicopathologic characteristics and survival in patients with GEC and BM and LC disease to date. Biomarker analysis reveals an enriched frequency of HER2 expression in BM, while this is uncommon in pts with LC. BM pts who were treated with surgery followed by radiation had a significantly improved OS. WBRT benefited patients with LC over palliative care alone. These findings add to our understanding for the management of this understudied population with poor survival. Research Sponsor: None.

<table>
<thead>
<tr>
<th>BM pts</th>
<th>Median Survival (months) (95%CI)</th>
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<tbody>
<tr>
<td>Palliative Care</td>
<td>0.76 (0.20, 4.26)</td>
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<tr>
<td>Radiation (WBRT/SRS)</td>
<td>3.8 (2.16, 5.85)</td>
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<tr>
<td>Surgery followed by Radiation</td>
<td>7.71 (5.76, 16.45)</td>
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<table>
<thead>
<tr>
<th>LC pts</th>
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<tr>
<td>Palliative Care</td>
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<tr>
<td>WBRT</td>
<td>2.7 (1.35, 6.0)</td>
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A radiomics model developed from pre-metastatic brain magnetic resonance imaging to predict brain metastasis in non–small-cell lung cancer: Evidence to the seed-and-soil theory.

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Background: Steven Paget’s “seed and soil” theory suggests that both the primary tumor and the target host organ play important roles in successful metastasis development. In this proof-of-concept study, we proposed that inter-individual differences exist in the brain’s congeniality for developing brain metastasis (BM), and validated the theory via developing a non-invasive radiomics BM prediction model.

Methods: 256 non-small cell lung cancer (NSCLC) patients with no BM at baseline brain magnetic resonance imaging (MRI) were selected, 128 patients developed BM within three years after diagnosis and 128 remained BM-free. For radiomics analysis, both the BM and non-BM groups were randomly distributed into training and testing datasets at an 70%:30% ratio. Baseline brain MRI (representing the soil) and chest computed tomography (CT, representing the seed) radiomics features were extracted to develop the BM prediction models. We first developed radiomics models using the training dataset and subsequently validated the models in the testing dataset. A radiomics BM score (RadBM score) was generated and BM-free survival were compared between RadBM score-high and RadBM score-low groups.

Results: The radiomics model developed from baseline brain MRI features alone can predict BM development in NSCLC patients. Furthermore, a fusion model integrating brain MRI features with primary tumor CT features (seed-and-soil model) provided synergetic effect and was more efficient in predicting BM (areas under the receiver operating characteristic curve 0.84[95% confidence interval: 0.80–0.89] and 0.80 [95% confidence interval: 0.71–0.88] in the training and testing datasets, respectively). BM-free survival was significantly shorter in the RadBM score-high group versus the RadBM score-low group (Log-rank P < 0.001). Cumulative BM rate at 3-year were 75.8% and 24.2% for RadBM score-high and RadBM score-low group, respectively.

Conclusions: The results demonstrated that intrinsic features of a non-metastatic organ exert a significant impact on metastasis development, which is first-in-class in metastasis prediction studies and provided novel evidence for the "seed-and-soil" theory of tumor metastasis. Radiomics BM prediction model utilizing both pre-metastatic brain and primary tumor features might provide a useful tool for identifying NSCLC patients more prone to develop BM and providing individualized management for these patients.

Research Sponsor: National Natural Science Foundation of China (81902973, 82001903); Beijing Xisikey Clinical Oncology Research Foundation (Y-2020Sciclone/qn-0041).
INTRAMET: Results of a prospective, single-arm, open-label phase II trial of intraoperative radiotherapy after resection of brain metastases.

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Background: Brain metastases (BM) occur in about 10-20% of all cancer patients during the course of their disease. The current standard of care for lesions that cause mass effects is neurosurgical resection followed by adjuvant radiotherapy of the resection cavity. We here report efficacy data of the INTRAMET trial (NCT03226483), which tested intraoperative radiation therapy (IORT) using a high-dose, single fraction to the tumor bed. Methods: Patients $\geq$18 years and Karnofsky (KPS) $\geq$50 with suspected BM were included. A frozen-section confirmed metastasis and technically applicable IORT were mandatory. Exclusion criteria were surgical or MRI contraindications, meningeal infiltration, or IORT Dmax doses exceeding 8 Gy at risk structures. IORT was performed after tumor resection in the operating room with a mobile low energy X-ray device emitting a spherical radiation field with a sharp dose gradient. A dose of 30 Gy was prescribed to the surface of the resection cavity. The primary endpoint was cumulative local control rate (LCR). Secondary endpoints were incidence of other (distant) BM (RCR), overall survival (OS), time to the next systemic treatment and adverse event rates (AE).

Results: In total, 35 of the originally 50 planned patients were recruited. After a pre-specified interim analysis, the study was prematurely halted due to good safety and outcomes profiles. 54.3% were men, the mean age was 64 (45-85) years. The mean follow-up was 25.7 (0.8-64.5) month. At the time of this report, 51.4% of patients were alive. 68.6% primary histologies corresponded to lung primaries. The LCR was 94.3% (95% CI 82.9-98.8%) and RCR was 57.1% (95% CI 40.7-72.4%), 8.6% patients or lesions developed out of field leptomeningeal progression. The mean OS was 37.4 months (95% CI 28.9-46.9). For those patients undergoing salvage whole brain RT (WBRT), the median initiation time was 147 (20-601) days with a significant survival benefit for those not requiring WBRT (p = 0.027). No significant survival differences were identified according to primary histology (p = 0.618), immunotherapy (p = 0.928), seizures at baseline (p = 0.169), KPS (p = 0.056) or radionecrosis appearance (p = 0.214). Mean time to next systemic treatment was 45.0 (95% CI 35.1-54.8) days. No G4-5 AE related to IORT occurred. The overall radionecrosis (RN) rate was 20% (n = 5 G1, n = 1 G2, n = 1 G3). No risk factors could be associated to RN. Post-surgical seizures were present in 28.6% patients, with eloquent localizations as the only predictive factor (p = 0.008). Conclusions: IORT for resected BM yields excellent local control rates and has a toxicity profile similar to those reported in post-operative SRS trials. By easing a prompt initiation of subsequent systemic treatments, IORT might shorten the overall treatment courses of many cancer patients. Clinical trial information: NCT03226483. Research Sponsor: None.

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Background: Data on the efficacy of immune checkpoint inhibitors on delaying or preventing the occurrence of brain metastases (BMs) in metastatic NSCLC without initial BMs is limited. We explored the benefit of first-line atezolizumab versus chemotherapy in the occurrence of BMs in patients without baseline BMs. Methods: Individual patient data from IMpower1301, IMpower131, and IMpower150 were pooled. All patients in the intention to treat population were analyzed. Primary endpoints included BM free survival (BMFS) and the cumulative incidence of BM. Patients without baseline BMs were categorized into two groups: patients who received treatment including atezolizumab (atezolizumab group) and patients who received comparator chemotherapies (chemotherapy group). Results: In 2543 patients without baseline BMs, 87 (3.4%) developed BM, including 58 (3.4%) and 29 (3.4%) in the atezolizumab group and the chemotherapy group, respectively. The median BMFS was 8.31 months (95% CI 7.79-8.67). The cumulative incidence of BM at 6 months, 12 months, and 24 months was 1.9%, 3.1%, and 3.8%, respectively. Compared to the chemotherapy group, BMFS was significantly improved in the atezolizumab group (8.6 months versus 7.3 months, p = 0.001). After taking the competing risk events into account, no significant difference of the cumulative incidence of BM was observed between the two groups (p = 0.671), suggesting that the significantly better BMFS in the atezolizumab group analyzed by Kaplan-Meier method should be due to the lower incidence of extracranial progression or death. Baseline bone metastasis and non-squamous NSCLC were identified as two risk factors for BM. Conclusions: In patients with NSCLC without baseline BMs, first-line atezolizumab improved BMFS but not the cumulative incidence of BM compared to chemotherapy, indicating that atezolizumab could not reduce the intrinsic risk of intracranial tumor spreading.

Research Sponsor: None.

Cumulative incidence (%) of BM for patients without baseline BMs.

<table>
<thead>
<tr>
<th>Time</th>
<th>All</th>
<th>Atezolizumab group</th>
<th>Chemotherapy group</th>
</tr>
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<tbody>
<tr>
<td>6 months</td>
<td>1.84</td>
<td>1.92</td>
<td>1.69</td>
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<tr>
<td>12 months</td>
<td>3.12</td>
<td>3.22</td>
<td>2.94</td>
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<tr>
<td>24 months</td>
<td>3.78</td>
<td>3.79</td>
<td>3.76</td>
</tr>
</tbody>
</table>

BM, brain metastasis.
The prognostic role of ventricular size and its dynamics in patients with leptomeningeal metastases from solid tumors.

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Background: Hydrocephalus is a common radiological sign in patients with leptomeningeal metastasis (LM) from solid tumors and can be assessed using the Evans index (EI) with high interrater agreement. Normal ranges of EI values have been defined as 0.27 ± 0.05 for females and 0.28 ± 0.06 for males aged 65-69 for the diagnostic work-up of dementia. Methods: We retrospectively assembled a cohort of 113 adult patients with a diagnosis of LM from solid extra-central nervous system tumors and explored the association of ventricular size assessed by the EI at diagnosis, of its modification between diagnosis and evaluation at first follow-up ( > 21 days after diagnosis), and at first progression, with outcome. Results: Median age was 58.2 years (interquartile range (IQR) 46.1-65.7), 41 patients (36%) were male, the most frequent cancers were lung cancer (n = 39, 35%), breast cancer (n = 36, 32%) and melanoma (n = 23, 20%). The median EI at baseline was 0.28 (IQR 0.26-0.31) and the EI value was 0.27 or more in 67 patients (59%) and 0.30 or more in 37 patients (33%). Among patients with MRI follow-up, the EI was increased in 19 of 47 patients (40%), including 9 of 47 patients (30%) and 10 of 47 patients (59%), respectively, without and with LM progression at first follow-up. At LM progression, an increase of EI was noted in 18 of 34 patients (53%). The median LM-specific progression-free (LM-PFS) survival was 1.8 months (IQR 0.8-3.7). The baseline EI was not significantly associated with LM-PFS (numerical values: p = 0.299). Median LM-PFS was 2.7 months (IQR 1.2-5.0) with an EI of 0.26 or less versus 1.3 months (IQR 0.6-3.1) with an EI of 0.27 or more (p = 0.296). It was 2.5 months (IQR 0.9-6) with an EI of 0.29 or less versus 1.1 months (IQR 0.5-2.4) with an EI of 0.30 or more (p = 0.147). An increase of 0.01 or more of the baseline EI first evaluation was associated with inferior LM-PFS (p = 0.007). The median overall survival was 2.9 months (IQR 1-7.2). The baseline EI was not associated with survival (p = 0.067), however, patients with a baseline EI of 0.26 or less had a longer survival than those with an EI of 0.27 or more (5.3 months, IQR 2.4-10.8, versus 1.3 months, IQR 0.6-4.1) (p = 0.006). Median survival was 3.7 months (IQR 1.4-8.3) with an EI of 0.29 or less versus 1.8 months (IQR 0.8-4.1) with an EI of 0.30 or more (p = 0.109). Among patients with follow-up scans available, median overall survival was 9.7 months (IQR 5.6-21.4) for patients with stable or decreased EI at first follow-up as opposed to 6.4 months (IQR 3.2-10.5) for those with an increase in the EI (p = 0.292). Conclusions: The EI at baseline is prognostic in LM on univariate analysis. An increase of EI during the follow-up is associated with inferior LM-PFS. Expanding the sample size and evaluation of confounding factors such as prior or concurrent treatment will help to better define the role of EI assessments in LM. Research Sponsor: None.
A systematic review and meta-analysis of intrathecal versus alternate routes of delivery for HER2-targeted therapies in patients with HER2+ breast cancer leptomeningeal metastases.

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Background: Patients with HER2+ breast cancer (BC) frequently develop leptomeningeal metastases (LM). While HER2-targeted therapies have demonstrated efficacy in the neoadjuvant, adjuvant, and metastatic settings, including for parenchymal brain metastases, their efficacy for patients with LM has not been studied in a randomized controlled trial. However, several single-armed prospective studies, case series and case reports have studied oral, intravenous (IV), or intrathecally (IT) administered HER2-targeted therapy regimens for patients with HER2+ BCLM.

Methods: We conducted a systematic review and meta-analysis of individual patient data to evaluate the efficacy of HER2-targeted therapies in HER2+ BCLM in accordance with PRISMA guidelines. Targeted therapies evaluated were trastuzumab (IT or IV), pertuzumab, lapatinib, neratinib, tucatinib, trastuzumab-emtansine (T-DM1) and trastuzumab-deruxtecan (TDXd). The primary endpoint was overall survival (OS), with progression-free survival (PFS) as a secondary endpoint. To assess differences between groups, shared frailty Cox regression models were used to estimate the hazard ratio (HR), 95% confidence interval (CI) and p-value.

Results: 7780 abstracts were screened, identifying 44 publications with 200 patients, corresponding to 257 lines of HER2-targeted therapy for BC LM which met inclusion criteria. In univariable (OS: HR=0.9, 95% CI: 0.64-1.4, P=0.76; PFS: HR=0.8, 95% CI: 0.57-1.2, P=0.35) and multivariable (OS: HR=1.4, 95% CI: 0.68-3.1, P=0.4; PFS: HR=0.8, 95% CI: 0.41-1.7, P=0.6) analyses, we observed no significant difference between IT, oral or IV administration of HER2-targeted therapy. Meanwhile, ECOG performance status remained independently associated with prolonged OS (HR=2.2, 95% CI: 1.5-3.2, P<0.001) and PFS (HR=2.2, 95% CI: 1.5-3.2, P<0.001 and HR=1.9, 95% CI: 1.4-2.8, P<0.001) in the final multivariable model. ECOG status was not associated with route of trastuzumab delivery (P>0.40). Anti-HER2 monoclonal antibody-based regimens did not demonstrate superiority over HER2 tyrosine kinase inhibitors (OS: P=0.647; PFS: P=0.983). In a cohort of 7 patients, TDXd demonstrated improved OS compared to other HER2-targeted therapies and compared to T-DM1 (P<0.05).

Conclusions: The results of this meta-analysis suggest that IT administration of HER2-targeted therapy for patients with HER2+ BCLM confers no additional benefit over oral and/or IV treatment regimens. We also present the first evidence supporting the efficacy of TDXd compared to alternative strategies for this patient population. Although the number of patients receiving TDXd in this cohort is small, this novel agent offers promise for this patient population and requires further investigation in prospective studies. Research Sponsor: None.
HER2-low breast cancer brain metastases: Incidence and treatment implications.

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Background: Brain metastases (BrM) are a major cause of morbidity and mortality among women with breast cancer (BC). Central nervous system (CNS)-penetrating systemic therapies for patients with HER2-negative BrM are lacking; this is particularly problematic for patients with triple negative disease (TNBC) who have a high likelihood of developing BrM. Given CNS activity of trastuzumab deruxtecan, efficacy for patients with HER2-low BrM is of interest. Methods: A retrospective study of two cohorts of patients who underwent surgery for BC BrM at Sunnybrook Health Sciences Centre between 1999-2013 and 2008-2018 were identified. Estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 (HER2) status were assessed based on 2018 ASCO/CAP guidelines. HER2-zero was defined as immunohistochemistry (IHC) 0; HER2-low was defined as IHC 1+ or IHC 2+ with fluorescence in situ hybridization (FISH) negative status. HER2-positive was defined as IHC 3+ or IHC 2+ with positive FISH. Clinicopathological features were recorded. We also assessed the prognostic association between extent of HER2 expression and i) brain-specific progression free survival (bsPFS), as well as ii) overall survival (OS).

Results: Out of 137 patients with resected BrM, tissue for HER2 assessment was available in 74.5% (n=102) of cases. In this cohort, the median age at BrM diagnosis was 53.5 (range, 32-85). 18.6% (n=19) had leptomeningeal disease and 68.6% (n=70) had extracranial disease. 53% (n=54) of the BrM were HER2-positive; 29.4% (n=30) were HER2-low and 17.6% (n=18) had HER2-zero status. Among BrM that were triple negative based on ASCO/CAP guidelines, 14 out of 22 cases (63.6%) were re-classified as being HER2-low. 15/25 (60%) BrM that were hormone receptor positive/HER2 negative (HR+/HER2-) based on ASCO/CAP guidelines were re-classified as being HER2-low. In total, 51 patients had matched primary breast and BrM tissue available; results of HER2 status when categorized as HER2-zero, HER2-low and HER2-positive were concordant in 82.3% (n= 42/51) of cases (Cohen’s kappa 0.58, p=0.0719). In 7 cases, the primary breast tissue was HER2-zero whereas the BrM was either HER2-low (n=5) or HER2-positive (n=2). In only one case (2%), expression of HER2 was lower in the BrM (HER2-low) compared to the primary BC (HER2-positive). Median time from primary BC to the development of BrM was 35 months (IQR, 14-69) in the overall cohort; patients with HER2-zero BrM had a numerically longer time to development of BrM (45.8 months), compared to those with HER2-low (35 months) and HER2-positive (35 months) BrM (p=0.948). There was no significant association between HER2-zero, HER2-low and HER2-positive status in BrM and either bsPFS or OS. Conclusions: Among patients with surgically resected BrM, a high proportion of those with metastatic TNBC and HR+/HER2-negative disease have “HER2-low” BrM with potential to benefit from HER2-targeted therapy. Research Sponsor: None.
Assessment of electronic health record (EHR)–based machine learning (ML) in predicting risk of brain metastasis among patients with early-stage non–small-cell lung cancer (eNSCLC).

Hossein Honarvar, Deep K Hathi, Ravi Bharat Parikh, Rahul K Das; ConcertAI, Cambridge, MA; Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: Among patients (pts) with eNSCLC, development of brain metastasis (BM) is a poor prognostic sign, but routine surveillance for BM is not recommended post-therapy. EHR-based ML algorithms may identify pts who would benefit from active brain MRI surveillance and/or treatment intensification in the early-stage setting. Methods: ConcertAI Patient360 database, consisting of structured and curated EHR records from pts receiving care in ~900 US oncology clinics, was used to identify pts diagnosed with stage IB-IIIA NSCLC without prior evidence of BM between Jan 2010 – December 2021. Presence of BM was identified from human curation of patient documents. Gradient boosting (GB), random forest (RF), and logistic regression (LR) algorithms with 3-fold cross-validation were trained and compared to predict risk of BM at two landmarks: 18 and 24 months (mos) from initial diagnosis (index). Pts who did not develop BM and either died or were lost to follow-up prior to landmark times were removed. Feature importance was defined using Shapley Additive Explanation (SHAP)-derived marginal odds ratios (OR). Due to low prevalence of BM, AUPRC was used as performance metric. Pts in the 1st and 4th quartiles of predicted probabilities from GB model were flagged as low-risk vs. high-risk. Results: Among 7473 pts in 18 mos model, median age was 68.4 years (IQR 13.2), 50.5% were female, and 10.9% were black. Demographics were similar for 6863 pts in 24 mos model. 6.4% and 8.3% developed BM at 18 and 24 mos. Ability of GB, RF, and LR models to predict BM was similar with validation AUPRC of 0.109 at 18 mos and 0.137 at 24 mos. In the GB model, BM prevalence in high-risk vs. low-risk group was 10.3% vs. 3.1% at 18 mos and 13.4% vs. 4.4% at 24 mos. In both landmark models, N0 stage and surgery within 90 days after index diagnosis were protective against BM, while presence of EGFR targetable mutations, adenocarcinoma (AD) histology, higher platelets (PLT), and history of pneumonia were risk factors. A glucose-by-histology interaction was found: For pts with normal blood glucose (GLU), risk of BM was independent of histology, for pts with high GLU, AD conferred greater risk of BM. Conclusions: An EHR-based ML model identified risk factors for developing BM among pts with eNSCLC and may identify pts who would benefit from active brain MRI surveillance and treatment intensification. Research Sponsor: ConcertAI.

<table>
<thead>
<tr>
<th>Feature</th>
<th>18-mos BM risk</th>
<th>24-mos BM risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>0.86 (0.61, 0.97)</td>
<td>0.86 (0.60, 0.99)</td>
</tr>
<tr>
<td>N0 stage</td>
<td>0.89 (0.69, 0.98)</td>
<td>0.87 (0.61, 1)</td>
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<tr>
<td>AD histology</td>
<td>1.14 (1, 1.45)</td>
<td>1.18 (1.18, 1.22)</td>
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<tr>
<td>EGFR exon 19 deletion or L858R</td>
<td>1.13 (1.15, 1.53)</td>
<td>1.15 (1.15, 1.53)</td>
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<tr>
<td>History of pneumonia</td>
<td>1.07 (1.124)</td>
<td>1.10 (1.14, 1.43)</td>
</tr>
<tr>
<td>PLT &gt; 330 vs &lt; 205 10^9/mL</td>
<td>1.06 (1, 1.31)</td>
<td>1.07 (1.13, 1.32)</td>
</tr>
<tr>
<td>Interactions % BM</td>
<td>GLU: histology</td>
<td>GLU ≥ 107: (AD = 11.4, (14.4, 6.7); non-AD = 6.0); (10.9, 10.8)</td>
</tr>
<tr>
<td></td>
<td>GLU &lt; 107: (8.2, 8.8)</td>
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</table>

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Large-scale clinicogenomic models of solid tumor CNS metastasis.

Justin Jee, Anisha Luthra, Christopher Fong, Karl Pichotta, Thinh Tran, Mirella Altoe, Alex Miller, Ronglai Shen, Michael F. Berger, Francisco Sanchez-Vega, Steven Brad Maron, Anton Safonov, Kenneth L. Kehl, Jorge S. Reis-Filho, Deborah Schrag, Sohrab P Shah, Pedram Razavi, Bob T. Li, Gregory J. Riely, Nikolaus Schultz; Memorial Sloan Kettering Cancer Center, New York, NY; Dana-Farber Cancer Institute, Boston, MA

Background: Central nervous system (CNS) metastasis is a major cause of cancer death and morbidity, but the clinicogenomic covariates of CNS metastasis have been studied in small cohorts. We sought to i) determine whether models predicting patient time to CNS metastasis (ttCNS) trained on a large, automatically annotated clinicogenomic dataset could stratify ttCNS risk in an external, manually curated cohort and ii) use these data to study the genomic risk factors for metastasis at scale. Methods: We leveraged the AACR Project GENIE Biopharma Collaborative (BPC), a structured curation of electronic health records at four cancer centers using the PRISSMM method, to train natural language processing (NLP) algorithms to annotate metastatic sites from radiology reports. We applied these algorithms to all reports for MSK patients with tumor sequencing with our FDA-authorized targeted sequencing platform. We used the resulting clinicogenomic data to train random survival forests (RSF) to predict radiographically confirmed ttCNS from time of sample acquisition for patients with non-small cell lung (NSCLC, N = 7,263), breast (BRC, N = 5,195; HR+ N = 4,050, HER2+ N = 879, triple-negative (TNBC) N = 866), and colorectal cancer (CRC, N = 4,320) using stage, gene-level pathogenic alterations, pre-existing metastatic sites, histopathology, prior and current treatment, and patient demographics as variables, excluding those reaching the endpoint prior to sample acquisition. We also predicted time to bone, liver, and adrenal metastases. RSFs were validated in the manually curated, non-MSK BPC cohort. Results: RSFs had predictive power for ttCNS in validation datasets (NSCLC c-index: 0.66, BRC: 0.71 (HR+ only: 0.71, HER2+ only: 0.69, TNBC: 0.62), CRC: 0.67, all p < 0.001). Pre-existing metastatic involvement, and genomic, histopathologic and clinical features had non-overlapping information for predicting ttCNS. We explored genomic covariates of ttCNS and other sites using Cox proportional hazards models adjusted for disease stage. Within individual cancer types, the hazard ratios of gene-level changes leading to the four considered sites of metastasis were correlated (Pearson R = 0.71-0.98); in all cancer types the highest correlations were between ttCNS and ttAdrenal metastases. Across cancer types, genomic alterations leading to metastatic sites were less correlated (R = -0.22-0.48). For example, CDKN2A/B and MYC alterations shortened ttCNS in NSCLC and HR+ BRC but not in HR- BRC. PTEN was associated with shortened ttCNS in TNBC and NSCLC but not CRC and other breast subtypes. Conclusions: Automatically annotated cohorts provide a means of studying drivers of metastasis at scale. Pre-existing non-CNS sites are associated with shorter ttCNS. Genomic alterations predisposing to CNS metastases frequently predispose to other organ metastases, although in general the genomics of organotropism are highly cancer-specific. Research Sponsor: U.S. National Institutes of Health.
Background: Surgically targeted radiation therapy (STaRT), using a novel bioresorbable collagen brachytherapy device containing 4 Cesium-131 sources, is FDA-cleared for use as adjuvant radiation therapy (RT) post-resection in both newly diagnosed and recurrent intracranial neoplasms. Intraoperative initiation of brachytherapy potentially minimizes post-resection tumor regrowth with a favorable dosimetric profile compared to external beam radiation. This work sought to determine early patterns of care and the safety of this approach in recurrent GBM. Methods: This prospective multi-institutional observational study (NCT04427384) included recurrent GBM patients who underwent maximum safe resection (MSR) and permanent implantation of the device(s) (GammaTile, GT Medical Technologies, Tempe, AZ, US). Descriptive and comparative analyses regarding patient characteristics and early clinical outcomes were performed. Toxicities were categorized using the CTCAE v5.0 adverse event (AE) criteria. Results: During 10/2020–01/2023, 14 participating sites enrolled 45 patients with recurrent GBM for STaRT; 2 patients had two sites treated for a total of 47 implants. 67% of patients were treated at the first recurrence, 24% at the second, and 13% at the third, respectively. The median age was 61 (range 28-75), 36% were female, and 23% were >65 years. 85% of patients received prior same-site RT with the median time from last RT to implantation of 14.6 months (range 3.5-57). The median maximum preoperative size was 4.2 cm (range 1.6-7.0) and the median volume was 20.8 cm³ (range 0.8-130). 68% of resections were gross-total, 17% near-total, and 15% sub-total; the median time needed for device implantation was 5 minutes (range 1.0-13). Median follow-up was 5.2 months (range 0.6-23.2). Median Karnofsky performance status (KPS) at screening, at initial postoperative assessment, and 3 months were all 80 (range 40-100). 7 attributed AEs occurred in 13% (6/45) of patients, all grade 3 AEs: 2 CSF leaks, 2 seizures, 1 cerebral edema, 1 pseudomeningocele, and 1 left hemiparesis. All except one were coded as related to both radiation and surgery; the patient with pseudomeningocele experienced a seizure at 47 days that was considered related to radiation alone. Conclusions: Early data from this prospective registry demonstrate the feasibility and safety of STaRT in recurrent GBM. Data on 6-month progression-free survival will be presented at the conference. A prospective randomized trial of adjuvant systemic therapy (AST) +MSR+STaRT versus MSR+AST is planned for initiation in 2023. Research Sponsor: GT Medical Technologies.
Multi-cancer brain metastasis risk score development and validation using 220,246 whole transcriptomes and machine learning.

Jim Abraham, Carey K. Anders, Adam Brufsky, Michael J. Glantz, Priscilla Kaliopi Brastianos, Luke Roy George Pike, Amy B. Heimberger, George W. Sledge, Matthew James Oberley, David Spetzler; Caris Life Sciences, Phoenix, AZ; Duke Cancer Institute, Durham, NC; Magee-Womens Hospital of UPMC/UPMC Hillman Cancer Center, Pittsburgh, PA; Penn State Milton S. Hershey Medical Center, Hershey, PA; Massachusetts General Hospital, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; NORTHWESTERN UNIVERSITY, Chicago, IL

Background: Brain metastases occur in multiple cancer types with higher prevalence in lung, breast, melanoma, and GI cancers. The prognoses of patients who develop brain metastases are very poor and identification of brain metastasis risk could be useful for prognostication, monitoring, and therapy selection. Methods: Data from the whole transcriptome of 220,246 tumor profiles were analyzed and multiple machine learning models were trained on various molecular subtypes. The dataset was split 50% for training and the other 50% for testing. UMAP was employed for dimensionality reduction and the patterns learned across the entirety of the training dataset irrespective of brain metastasis were leveraged on the testing data set. Patients with brain metastasis were identified using the presence of ICD-10 code C79.31 (Secondary malignant neoplasm of the brain). As the absence of C79.31 could be due to the event not happening yet, patients without brain metastasis were stratified into groups based on 3, 4 or greater than 5 years without a C79.31 ICD-10 code. The brain metastasis risk score was defined by empirical evaluation of the positive predictive value in 7 groups of risk probabilities. The validation set contained 1,217 patients with brain metastasis and 4,631 without an observed brain metastasis within 3 years. Results: In the validation set, the prevalence of brain metastases within the risk scores across all cancer types ranged from 4% with the lowest risk score to 94% in the highest with 71% of cases receiving the lowest 2 risk scores, 15% the 2 intermediate risk scores, and 14% the 3 highest risk scores. For breast, lung and colon cancers, the prevalence of brain metastasis ranged from 4-10% in patients with the lowest risk scores to 92-100% in patients with the highest however the distribution of cases with each risk score was markedly different across cancer type. Breast cancer had 62% of cases receiving the lowest 2 risk scores versus 27% in lung, and 92% in colon. Breast cancer had 18% of cases receiving the 3 highest risk scores while lung had 42% and colon only 2% of cases with those 3 highest scores. Conclusions: Whole transcriptome data can be leveraged by a machine learning platform that employs dimensionality reduction techniques along with transfer learning to predict the risk of brain metastasis. This tool can be used to augment the clinical picture of cancer patients an unmet clinical opportunity to inform prognosis, monitoring, and therapeutic selection.

Research Sponsor: None.

Likun Chen, Meichen Li, Jing Chen, Hui Yu, Baishen Zhang, Xue Hou; Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; Sun Yat-sen University Cancer Center, Guangdong, Guangdong, China; Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China; Sun Yat-Sen University Cancer Center, Guangzhou, Guangdong, China; Department of Medical Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, Guangdong, China

Background: Immunotherapy has been the standard first-line therapy in patients with advanced non-small cell lung cancer (NSCLC), and shown a certain efficacy for patients with brain metastases. However, the appropriate predictive biomarkers for intracranial tumor response to immunotherapy are unclear. We conducted this prospective study to explore the immunological cytokines in cerebrospinal fluid (CSF) to predict intracranial tumor response to immunotherapy in NSCLC patients with brain metastases.

Methods: We prospectively enrolled treatment-naive, EGFR/ALK wild-type NSCLC patients with brain metastases in this study. Patients received chemotherapy plus camrelizumab (a humanized anti-PD-1 monoclonal antibody) as first-line treatment, and paired plasma and cerebrospinal fluid (CSF) samples were collected at baseline and first treatment evaluation (8-week). All samples were detected for 92 Immuno-Oncology cytokines using the Olink panels, and were explored for predictive biomarkers to immunotherapy. The Mann-Whitney U test was performed to compare the immunological cytokine expression between intracranial response and non-response groups. And logistic LASSO regression model was used to variate selection and develop a CSF immuno-cytokine model to predict intracranial tumor response.

Results: Between April 2020 and May 2022, a total of 28 patients were enrolled this study. At baseline, most immunological cytokines were significantly lower in paired CSF than in plasma, whereas a subset including CD83, PTN, TNFRSF21, TWEAK, ICOSLG, DCN, IL-18 and MCP-1 were increasing expressed in CSF samples. For patients with objective intracranial tumor response compared to patients with non-response, the baseline CSF levels of LAMP3 were significantly higher, whereas the CXCL10, IL-12, CXCL11, IL-18, TIE2, HGF and PDCD1 levels were significantly lower. And patients with lower HGF, IL-18 or PDCD1 levels had significantly longer intracranial progression-free survival to immunotherapy. The above CSF immunological cytokines were significantly decreased at first treatment evaluation in patients with intracranial tumor response. Our logistic CSF immuno-cytokine model selected TIE2, IL-18, LAMP3, PDCD1 and IL-12 that were significantly associated with intracranial tumor response, and yielded a mean AUC of 0.91, compared to PD-L1 expression (mean AUC of 0.72).

Conclusions: Immunological cytokines in CSF could predict intracranial tumor response to immunotherapy in NSCLC patients with brain metastases, and findings require validation in a larger prospective cohort. Research Sponsor: None.
Analysis of tumor progression among patients with glioma after COVID-19 infection.

Tim Gregory, Stephanie Knight, Ashley Aaroe, Barbara Jane O’Brien, Chirag B Patel, Shiao-Fei S. Weathers, Nazanin Majd, Vinay K. Puduvalli, Carlos Kamiya-Matsuoka; University of Texas MD Anderson Cancer Center, Houston, TX; MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: As of January 2023, there have been 6.7 million worldwide deaths attributed to SARS-CoV-2 COVID-19, which has impacted outcomes and medical care for all patients. Relatively little is known about the direct effects mediated by the virus on CNS tumor biology, despite the fact that viral neurotropism is well described, various coronavirus receptors have been observed in glioblastoma (GBM) tissues, and differential monocytic infiltration has been proposed to dysregulate the immune microenvironment. We detected a trend of rapid progression following COVID-19 infection among several patients with primary brain tumor patients and sought to systematically evaluate the pace of progression among infected patients in our institution. Methods: A single-institutional database of COVID-19 patients and an electronic medical record (EMR) search tool were used to identify a total cohort of 67 patients with glioma for retrospective analysis. This included 38 GBMs, 18 IDH-mutant gliomas, 5 ependymomas, 2 pilocytic astrocytomas, 1 diffuse midline glioma, 1 diffuse hemispheric glioma, and 1 ganglioglioma patients, each of whom had a documented COVID-19 infection between June 2020-December 2022. Hyperprogression was defined as tumor increase ≥40% compared to previous scan using RECIST size criteria. Results: Thirty-nine (58%) patients experienced tumor progression following COVID-19 infection at a median of 34 days (range=1-734 days) after testing positive for COVID-19. Twenty-two (56%) had received COVID-19 vaccine before their infection and 5 (13%) had asymptomatic infections. Twenty-two patients had measurably increased tumor area by a median of 63% (range=10-2,900%), 18 of which constituted hyperprogression; 16 patients developed multifocal disease, 8 developed new nodular enhancement, 3 developed leptomeningeal disease (LMD), and 2 experienced increased infiltrative disease alone. Ten patients’ presentation with new glioma was preceded by COVID-19 infection by a median of 31 days. GBM patients represented the majority of progression events, among whom 59% progressed within 60 days of documented infection (median 25 days). This subgroup of GBM with rapid progression within 60 days had a mOS from infection of 5.2 months; 89% had TERT promotor mutations and 42% had MGMT promoter methylation. Conclusions: Glioma patients appear to have disease progression at an accelerated pace in the first two months after COVID-19 infection. This suggests that glioma patients should continue observing strict precautions to prevent infection and should be clinically monitored vigilantly after infection, with consideration for short interval imaging during treatment. These preliminary data warrant further investigation exploring changes of immune cell infiltration in the tumor microenvironment and the possible correlation between tumor progression and COVID-19. Research Sponsor: None.
Safety, efficacy, and biomarker analysis of response to engineered tumor-infiltrating lymphocytes secreting anti-PD-1 antibody in recurrent glioblastoma: An open-label, two-arms, phase 1 study.

Yu Yao, Di Chen, Chao Tang, Chunxia Ji, Zhong Li, Qijun Qian; Department of Neurosurgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China; Center for Clinical Development and Research, Pharmaceutical Technology Inc, Shanghai Cell Therapy Group, Shanghai, China; Shanghai Mengchao Cancer Hospital, Shanghai University, Shanghai, China

Background: Adoptive cell therapy using tumor-infiltrating lymphocytes (TILs) is effective against solid tumors with convincing evidence. But T-cells infused were exhausted when they encountered PD-1-mediated immunosuppression in the microenvironment. Here, we generated a modified autologous TILs secreting antibody targeting PD-1 (PD1-TIL), and conducted a first-in-human, two arms, phase 1 study (NCT03347097) in recurrent glioblastoma who had a poor prognosis with estimated 6-9 months of median overall survival (OS). Methods: Patients were included to be treated with PD1-TIL or TIL cell products intravenously every one month following surgery. The primary endpoint was safety and feasibility. The secondary endpoints were disease control rate (DCR), OS, immunologic responses and biomarker analysis. The clinical response to cell therapy was assessed by MRI according to iRANO criteria. Here, patients with clinical benefit (CR, PR, and SD) were defined as responder. Results: A total of 21 consecutive patients (median age 45 years, range 20–64) received infusions of cell products (7 patients for PD1-TIL with 1 excluded, 14 patients for TIL with 2 excluded). 52% (11/21) and 29% (6/21) of 21 patients had methylated MGMT promoter and IDH1/2 mutant respectively. No significant differences in baseline characteristics between groups were found. Both of PD1-TIL and TIL infusions were well tolerated with no unexpected high-grade adverse events. Of 7 evaluable patients in PD1-TIL group, 1 had PR for more than 26 months, 2 had SD lasting for 7.7 months and 24 months, and 4 had PD after infusion. The DCR, 1-year and 2-years survival rates in PD1-TIL group were 43% (3/7), 86% (6/7) and 29% (2/7) respectively. In TIL group, 3 patients had SD and the others had PD. The DCR, 1-year and 2-years survival rates in TIL group were half of that in PD1-TIL group. Survival analysis showed that patients treated by PD1-TIL had extended OS than those received TIL (16.1 vs. 11.2 months, P = 0.047). Among 21 patients, clinical responders had significantly improved OS (30.9 vs. 10.7 months, P = 0.001) than non-responders. We also found a high capacity for engraftment and persistence of infused TILs in peripheral blood which could be detectable at 6 months after treatment. Existence of neoantigen-reactive T cell clonotypes in cell products may be important for responding because missing of missense mutations predicted to generate a neoantigen after cell therapy was a remarkable signature in responders. Responsive tumors were also associated with tumor microenvironment profiles. Conclusions: This first-in-human study establish the preliminary feasibility, safety and encouraging efficacy of PD1-antibody-secreting TILs, and may constitute a new treatment strategy by T-cell genetic engineering in glioblastoma. Clinical trial information: NCT03347097. Research Sponsor: National Key R&D Program of China; National Natural Science Foundation of China.
An exploratory clinical trial on intra-lumbar injection of B7H3-specific allogeneic universal CAR-T cells in patients with recurrent high-grade gliomas.

Xiaoyun Shang; T-MAXIMUM Pharmaceutical (Suzhou) Co., Ltd., Suzhou, China

Background: No standard-of-care treatment was established for recurrent high-grade gliomas (rHGGs) yet. Intrathecal infusion of autologous chimeric antigen receptor-T (CAR-T) cells has displayed potent anti-tumor activity in one patient (Brown et al. N Engl J Med 2016). We evaluated the safety, efficacy, pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of B7H3-specific allogeneic universal CAR-T (B7H3 UCAR-T) cells in patients with rHGGs. Methods: Eligible patients who had received standard treatment for newly-diagnosed high-grade gliomas but failed were treated with \(2.5 \times 10^7\) B7H3 UCAR-T cells via intra-lumbar injection every month. Eligibility criteria included histologic and/or cytologic rHGGs, B7H3-positive antigen expression rate of \(>50\%\) in tumor tissue and Karnofsky performance status (KPS) \(\geq 40\). The primary endpoint was treatment-related adverse events (TAEs); secondary endpoints include overall survival (OS) and objective response rate (ORR); exploratory endpoints were PK and PD characteristics of B7H3 UCAR-T cells. Results: In the 7 patients enrolled, 4 (57.1\%) were female, 5 (71.4\%) glioblastoma (WHO Grade IV) and 2 (28.6\%) diffuse midline glioma (WHO Grade IV), and the mean age was 40.4 years. The most common reported TAEs were increased cerebrospinal fluid (CSF) IL-6 (7/7, 100\%), headache (7/7, 100\%), increased blood IL-6 (6/7, 86\%) and fever (6/7, 86\%). No adverse events of grade 3 or greater related to B7H3 UCAR-T cells were reported. All the adverse events recovered or relieved after treatment. No typical or severe systemic cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) or graft versus host disease (GvHD) were observed during the study period. Based on Immunotherapy Response Assessment in Neuro-Oncology (iRANO), 3 of 7 patients had response to therapy (42.9\%; 95\% CI: 15.8 to 75.0) and 7 of 7 patients were stable disease (100\%; 95\% CI: 64.6 to 100). As of cutoff date (January 30, 2023), two patients died. The median OS was not reached (95\% CI: 12.9 to could not be estimated). The median follow-up for OS was 15.6 months (95\% CI: 14.7 to 16.1). OS rate at 12 months was 85.7\% (95\% CI: 48.7 to 97.4). The CAR DNA copy numbers increased 1 day after each administration and persist at least 1 month in cerebrospinal fluid. IL-6 concentrations in CSF and peripheral blood increased after each administration while the change and concentration values in peripheral blood were much lower than those in CSF. Conclusions: In patients with rHGGs, B7H3 UCAR-T cells was not associated with any toxic effects of grade 3 or higher. B7H3 UCAR-T cells resulted in a significantly longer overall survival and a higher objective response rate than history data. B7H3 UCAR-T cells persist well in patients. Clinical trial information: ChiCTR2100047968. Research Sponsor: T-MAXIMUM Pharmaceuticals (Suzhou) Co., Ltd.
Lisavanbulin in patients with recurrent glioblastoma: Phase 2a results and a consolidated analysis of response-predictive biomarkers.

Juanita Suzanne Lopez, Simon Haefliger, Ruth Plummer, Paul M. Clement, Heinz Philipp Laubli, Patrick Roth, T.R. Jeffry Evans, Lucy Brazil, Ghazaleh Tabatabai, Antje Wick, Wing Hing Hing Yau, Benjamin Wunderlich, Kirk Beebe, Joel Robert Eisner, Marc Engelhardt, Thomas Kaindl, Peter Hau, Thomas Hundsberger, Joachim Steinbach; The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Inselspital, Bern University Hospital, University of Bern, Department of Medical Oncology, Bern, Switzerland; Newcastle University and Northern Centre for Cancer Care, Freeman Hospital, Newcastle upon Tyne, United Kingdom; UZ Leuven - Leuven Cancer Institute - KU Leuven, Leuven, Belgium; University Hospital Basel, Basel, Switzerland; University Hospital Zurich and University of Zurich, Zürich, Switzerland; University Hospital Regensburg, Regensburg, Germany; Department of Neurology and Medical Oncology, Cantonal Hospital St. Gallen, Sankt Gallen, Switzerland; Neurology and Neuro-Oncology Department, Universitätsklinikum Frankfurt (Johann-Wolfgang Goethe-Universität), Frankfurt, Germany

Background: Lisavanbulin (BAL101553, prodrug of BAL27862) destabilizes microtubules and promotes tumor cell death by modulating the spindle assembly checkpoint. BAL27862 is a lipophilic small molecule shown in rodents to penetrate the brain, with antitumor activity in orthotopic glioblastoma (GBM) models. In the Phase 1 part of this study, 2 of 5 patients with recurrent IDH-mutated G4 astrocytoma treated at active dose levels (15–30 mg/day) showed long-lasting objective responses and strong end-binding protein 1 (EB1) expression in GBM tissue by IHC. EB1 is a regulator protein on microtubules.

Methods: The objective of the Phase 2 study was to investigate prospectively the response-predictive value of EB1, and to identify RNA-based response signatures in patients with recurrent GBM. A Simon’s two-stage design was used with an objective response rate (ORR) ≥ 2/9 required in Stage 1 to enable a final ORR ≥ 6/19. A prescreening program identified patients with EB1-positive archival GBM tissue. All patients received 25 mg oral lisavanbulin once daily. RNA-seq was performed on archival GBM tissues.

Results: GBM tissue samples from 64 of 629 patients (10.2%) obtained from 13 sites in four countries were EB1-positive, and 18 of these patients received lisavanbulin. Of 9 patients with measurable disease evaluable for response in Stage 1, one patient had a partial response, and another had a 44% target lesion area reduction. Despite sustained activity in these patients, formal stage transition criteria were not met, and the study was closed. IHC testing for EB1 did not show sufficient enrichment for response, but it is thought that IDH status may play a role. In addition, RNA-seq analyses identified a five-gene signature that is distinct from expression patterns observed with EB1-IHC positivity, and predicts current responses irrespective of IDH status. This signature is characterized by homeobox gene downregulation, which may be implicated in the control of microtubule dynamics.

Conclusions: This Phase 2a study supports previous study results that lisavanbulin is associated with durable responses and clinical benefit in a subset of patients with GBM. RNA-seq analyses of GBM samples suggest further evaluation of the lisavanbulin predictive response signature.

<table>
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<tr>
<th>Study phase and tumor characteristics of patients with GBM or G4 astrocytoma</th>
<th>Number of patients treated with 15–30 mg/day lisavanbulin</th>
<th>Number of patients with Objective response</th>
<th>Best response and treatment duration (months) in patients ongoing on 31 Dec 2022</th>
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<td>Phase 1, IDH mut</td>
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<td>Phase 2, IDH wt, non-evaluable</td>
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A single-arm, phase 2 clinical trial of abemaciclib in adult patients with recurrent grade 3 oligodendroglioma.


Background: Oligodendroglioma is a malignant glial neoplasm arising primarily in young adults. Although radiotherapy (RT) and chemotherapy result in durable disease control, tumor recurrence is inevitable and life-limiting. The cyclin D1-CDK4 axis is frequently dysregulated in recurrent oligodendroglioma. Abemaciclib is a selective CDK4/6 inhibitor that has been shown to achieve pharmacologically-relevant concentrations in brain tumor tissue. Methods: We conducted a single-center, single-arm, phase 2 trial evaluating the efficacy of abemaciclib in patients with recurrent oligodendroglioma, IDH-mutant and 1p/19q-codeleted, WHO Grade 3, following prior RT and ≥ 1 line of alkylating chemotherapy. Patients received abemaciclib 200mg twice daily. Primary endpoint was progression-free survival status at 6 months (PFS-6). Ten patients were needed for 80% power to detect the difference between the null (PFS-6 = 50%) and alternative (PFS-6 = 85%) hypotheses; one-sided \( \alpha = 0.05 \). Modified RANO criteria were used for patients with enhancing tumors and RANO low-grade glioma criteria for patients with nonenhancing tumors. Results: Between November 2019 - August 2022, 10 patients were enrolled (Baseline Characteristics). Most common treatment-related adverse event (trAE) was grade 1-2 diarrhea, occurring in all 10 patients. Grade 3-4 trAEs included grade 4 thrombocytopenia (n=2), grade 3 neutropenia (n=1), grade 3 fatigue (n=2), and grade 3 ALT increase (n=1). In patients with enhancing tumor (n=9), best response was partial response in 2 patients (ORR=22.2%; DOR 13.1 and 7.7 months, respectively), stable disease (SD) in 3 patients (33.3%; duration of SD 17.0, 6.7, and 2.5 months, respectively), progressive disease in 3 patients (33.3%), and not evaluable in 1 patient (11.1%). In the patient with nonenhancing tumor, best response was SD (duration 10.2 months). Median PFS was 7.7 months (95% CI, 1.7 – 13.1 months); median overall survival was not reached (median follow-up 17 months). The study’s primary endpoint was not met; 5/10 patients (50%) were alive and progression-free at 6 months, below the minimum required (8/10) to consider abemaciclib worthy of further investigation. Conclusions: Despite objective responses and durable disease control in a small subset of patients, the efficacy of abemaciclib in recurrent grade 3 oligodendroglioma was not adequate to warrant further clinical evaluation of abemaciclib monotherapy in unselected patients. Correlative studies are ongoing to identify which patients with oligodendroglioma may benefit from abemaciclib. Clinical trial information: NCT03969706. Research Sponsor: Eli Lilly.

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Phase I/IIa study of concomitant radiotherapy with olaparib and temozolomide in unresectable high grade glioma patients: OLA-TMZ-RTE-01.

Dinu Stefan, Justine Lequesne, Sunyach Marie, Delphine Larrieu-Ciron, Charlotte Bronnimann, Loic Feuvret, Julien Geffrélot, Jeanne Riverain, Pierre-Emmanuel Brachet, Joëlle Lacroix, Fernand Missohou, Maxime Faisant, Evelyne Emery, Elisabeth Moyal, Bérénice Legrand, Gwenaelle Boudier, Marie Castera, Jean-Michel Grellard, Paul Lesueur, Benoîte Clarisse; Centre François Baclesse, Radiation Oncology Department, Caen, France; Centre François Baclesse, Clinical Research Department, Caen, France; Centre Léon Berard, Radiation Oncology Department, Lyon, France; Cancer University Institute of Toulouse - Oncopole, Toulouse, France; University Hospital, CHU Bordeaux, Radiation Oncology Department, Bordeaux, France; Hospices Civils de Lyon (HCL), Groupe Est, Lyon, Lyon, France; Centre François Baclesse, Department of Medical Oncology, Caen, France; Centre François Baclesse, Radiology Department, Caen, France; University Hospital, Caen, Department of Pathology, Caen, France; University Hospital, Department of Neurosurgery, Caen, France; Institut Universitaire de Cancer de Toulouse-Oncopole, Caen, France

Background: Although the Stupp protocol (radiotherapy + temozolomide (TMZ)) remains the mainstay of glioblastoma (GBM) first line treatment after extended surgery, the prognosis is still poor. PARP inhibitors, such as olaparib, may improve GBM outcomes by enhancing cytotoxic effects of ionizing radiation and TMZ. The non-dividing nature of normal brain cells allows a dedicated tumor radiosensitization. We implemented a phase I/IIa trial to assess safety and efficacy of olaparib combined with TMZ concomitant with intensity modulated radiotherapy (IMRT) as a first line treatment in unresectable GBM patients (pts). We herein present results of the phase I step. Methods: Based on the Stupp protocol, 2 treatment periods were considered. The radiotherapy period (RT) occurs after surgery: pts received IMRT (60 Gy/30 fractions/6 wks), oral TMZ (75 mg/m²) during IMRT, and olaparib orally given at the same dose until 4 wks after the end of IMRT. For the maintenance period (MT) from 4 wks after IMRT, pts received TMZ (150 mg/m², days (D) 1-5 every 28 days, for 6 cycles) plus olaparib at the MT dose level up to disease progression or unacceptable toxicity. The phase I included 2 sequential dose escalations (DE1, DE2) of olaparib to split both periods for DLT (Dose Limiting Toxicities) assessment. Olaparib dose levels (DL) were: 50 mg Q12H D 1-3 (DL1), 100 mg Q12H D1-3 (DL2) or D1-5 (DL3), 200 mg Q12H D1-3 (DL4) or D1-5 (DL5) or 200 mg Q12H continuously (DL6). Pts in DE1 received olaparib only during RT to determine the MTD1 (Maximum-Tolerated Dose), by assessing DLT on this period. Next, after olaparib administered at MTD1 during RT, pts in DE2 received olaparib during MT to determine MTD2 (=MTD1) during the MT period, assessing DLT from the first 2 cycles. DE1 and DE2 were performed by a TITE-CRM (Time-To-Event Continual Reassessment Method). Results: From 2017 to 2021, 30 pts were enrolled: 20 (67%) men, median age 59 yrs [range 25-70]. 16 and 11 pts were assessable for determining MTD1 and MTD2, respectively. In DE1, 2 pts received olaparib at DL1, 6 at DL2, 6 at DL3, 1 at DL4 and 1 at DL5. 4 pts observed DLT (3 at DL3, 1 at DL5): thrombocytopenia G3-4 (n=4) + neutropenia G4 (n=2). MTD1 was defined as DL2 with estimated probability of DLT of 22.1% [95%CI 8-40.5]. In DE2, 2 pts were treated at DL1, 9 at DL2. 1 pt observed DLT at DL2: thrombocytopenia G4. MTD2 was defined as DL2 with estimated probability of DLT of 13.3% [0.2-0.35]. No interruption of IMRT for toxicity was observed. Excepted DLT, permanent olaparib discontinuation for toxicity was observed in 1 pt during RT and 2 pts during MT. Toxicity induced temporary TMZ interruption in 4 pts, none with permanent discontinuation. No toxic death was observed. Conclusions: Olaparib 100 mg Q12H D1-3 in concomitant with the Stupp protocol has an acceptable safety profile in unresectable GBM pts: it warrants efficacy determination, in the ongoing phase IIa step. Clinical trial information: NCT03212742. Research Sponsor: French Cancer Institute and French Health Ministry (ref: PHRC-K15-135, INCa-DGOS_9780); Astra-Zeneca for Olaparib supply.
Final results of phase 2 trial of personal dendritic cell (DC) vaccines loaded with autologous tumor antigens (ATA) in newly diagnosed glioblastoma (GBM).

Daniela Annenelie Bota, David Eric Piccioni, Thomas H. Taylor, Renato V. LaRocca, Robert D. Aiken, Xiao-Tang Kong, Katrina L. Lopez, Hans S. Keirstead, Gabriel I. Nistor, Robert O. Dillman; University of California Irvine, Irvine, CA; University of California San Diego, La Jolla, CA; University of California Irvine Department of Epidemiology and Biostatistics, Irvine, CA; Norton Cancer Institute, Louisville, KY; Rutgers Cancer Center, New Brunswick, NJ; UCI Health, Orange, CA; AIVITA Biomedical, Inc., Irvine, CA; AIVITA Biomedical, Irvine, CA; Aivita Biomedical, Inc., Irvine, CA

Background: Standard GBM therapy is associated with early progression and poor overall survival (OS). DC-ATA AV-GBM-1, a personal vaccine consisting of autologous DC pulsed with ATA, was investigated in a multicenter trial in patients with newly diagnosed GBM.

Methods: Key eligibility criteria for surgical collection of tumor were clinical suspicion of new primary GBM & age 18-70 years. ATA lysate was prepared from irradiated tumor cells that were self-renewing in serum-free media. Autologous monocytes (MC) were collected by leukapheresis. Prior to initiating concurrent radiation therapy (RT) and temozolomide (TMZ), patients were enrolled with intent-to-treat (ITT) with DC-ATA after RT/TMZ. Eligibility included confirmation of primary GBM, availability of ATA & MC, KPS > 70 and plans for RT/TMZ. DC-ATA was manufactured during RT/TMZ. MC were differentiated into DC by culturing with IL-4 & GM-CSF, then DC were incubated with ATA. DC-ATA was suspended in 500 mg GM-CSF just prior to s.c. injections at weeks 1, 2, 3, 8, 12, 16, 20, & 24 (8 doses). Patients were not excluded based on apparent disease progression or PFS. Standard adjuvant TMZ regimens were started after the 3 weekly injections. Primary endpoint was > 75% OS 14.6 months from ITT enrollment. Secondary endpoints included median OS & progression-free survival (PFS).

Results: Cell line and MC collection were successful for 97% of patients. Median age of the 60 ITT enrollees was 59 years. 3 patients withdrew before starting DC-ATA; 57 received 392 injections; 68% received all 8. Most common AE attributed to DC-ATA were local injection site reactions (16%) & flu-like symptoms (10%), but 33% experienced seizures. After 3 years of follow up, OS at 14.6 mos is 52.7% (95% CI 39.8,65.8), median OS 16.0 mos (95% CI 12.9,21.7) & median PFS 10.4 mos (95% CI 8.6,11.6). OS rates at 1, 2, & 3 years are 70.1%, 32.4%, & 23.2%. Longer OS was associated with 8 DC-ATA doses (p < 0.0001), on < 2 mg/day dexamethasone (dex) at start of DC-ATA (p = 0.005), > 6 cycles of adjuvant TMZ (p = 0.0054), & KPS 90 or 100 (p = 0.010) at enrollment. Independent variables per multivariate Cox regression analysis were 8 DC-ATA doses, dex dose, IDH mutated, TMZ > 6 cycles, & MGMT promoter methylated.

Concurrent TMZ regimens included TMZ alone (n = 28), TMZ + anti-VEGF(n = 14), & TMZ + tumor treating fields (TTF) (n = 10); 8 received no concurrent TMZ. OS was longer in patients treated with concurrent TMZ alone compared to no TMZ (p = 0.0003), TMZ + anti-VEGF (p = 0.045) or TMZ + TTF (p = 0.045). The only common features among 7 patients progression-free at 3 years are 8 DC-ATA injections, age < 60, & < 2 mg dex. Conclusions: DC-ATA was reliably produced and injections well-tolerated in combination with various TMZ-based regimens, but the primary OS objective was not achieved. PFS was encouraging, but did not translate into improved OS, perhaps because DC-ATA was limited to 8 injections. Clinical trial information: NCT03400917. Research Sponsor: AIVITA Biomedical, Inc.
Potential predictive biomarker for response to radiotherapy and CXCL12 inhibition in glioblastoma in the phase I/II GLORIA trial.

Frank Anton Giordano, Julian Philipp Layer, Sonia Leonardelli, Lea Lydia Friker, Roberta Turiello, Dillon Corvino, Thomas Zeyen, Christina Schaub, Wolf Mueller, Elena Sperk, Leonard Christopher Schmeel, Katharina Sahm, Sied Kebir, Peter Hambsch, Torsten Pietsch, Sotirios Bisdas, Martin Glas, Clemens Seidel, Ulrich Herrlinger, Michael Hölzel; Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany; Department of Radiation Oncology and Institute of Experimental Oncology, University Hospital Bonn, Bonn, Germany; Institute of Experimental Oncology, University Hospital Bonn, Bonn, Germany; Department of Neuroradiology, University Hospital Bonn, Bonn, Germany; Division of Clinical Neuro-Oncology, Department of Neurology, University hospital Bonn, Bonn, Germany; Division of Neurooncology, Department of Neurology, University Hospital Bonn, Bonn, Germany; Institute of Neuropathology, University Hospital Leipzig, Bonn, Germany; Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; Department of Radiation Oncology, University Hospital Bonn, Bonn, Germany; Department of Neurology, University Hospital Mannheim, Mannheim, Germany; Division of Clinical Neurooncology, Department of Neurology, University Hospital Essen, Essen, Germany; Department of Radiotherapy, University Hospital Essen, Essen, Germany; University College London, London, United Kingdom; Division of Clinical Neurooncology, Department of Neurology, University Hospital Essen, University Duisburg-Essen, West German Cancer Center (WTZ) and German Cancer Consortium, Partner Site, Essen, Germany; Department of Radiotherapy, University Hospital Leipzig, Leipzig, Germany; Division of Clinical Neuro-Oncology, Department of Neurology, University Hospital Bonn, Bonn, Germany

Background: Standard of care (SOC) treatment achieves poor clinical outcomes in patients with glioblastoma (GBM), particularly in the absence of MGMT promoter hypermethylation. Preclinical models suggest that GBM recurrence is facilitated by CXCL12-mediated recruitment of bone marrow-derived cells capable of vasculogenesis after radiotherapy (RT). We have recently reported favorable safety and feasibility data of the phase I/II GLORIA trial, which combines RT and the CXCL12-neutralizing L-RNA aptamer olaptesed pegol (NOX-A12) in patients with newly diagnosed, incompletely resected or unresected GBM lacking MGMT promoter hypermethylation (NCT04121455). Here we report on clinical outcomes and their correlation with potential biomarkers.

Methods: 10 patients with newly diagnosed incompletely resected (n=8) or biopsied (n=2) GBM with ECOG ≤2, age ≥18 and without MGMT promoter hypermethylation were enrolled. All patients received standard RT (60 Gy in 30 fractions or 40.05 Gy in 15 fractions) and escalating dose levels of continuous (24/7) i.v. infusions of NOX-A12 for 26 weeks. While the previously reported primary endpoint was safety, secondary efficacy endpoints included progression-free survival (PFS) and overall survival (OS). Biomarker assessment was performed with a six-plex immunofluorescence staining (CODEX) of neuropathologically confirmed tumor areas of pretreatment tissues for CXCL12, CD31 (endothelial cells), GFAP (glioma cells), CD68 (macrophages, microglia), aSMA (pericytes), Ki-67 (proliferating cells) and a nuclear marker. An independent patient cohort treated with SOC (n=15) matched by clinical and histopathological features was used for comparisons of efficacy and biomarker assessment.

Results: Median PFS of the GLORIA cohort was 5.7 (range 1.9–8.5) months and the median OS was 12.7 (4.7–18.4) months. Biomarker analyses revealed that a higher frequency of CXCL12 expressing endothelial and glioma cells (EG12 score) significantly correlated with PFS (r=0.87; p=0.005) in patients treated with RT and NOX-A12, but not with SOC (r=−0.10; p=0.724). GLORIA patients with a high EG12 score (median classifier) had a significantly longer PFS than those with lower scores (3.0 vs. 6.0 months; p=0.031) and a trend towards prolonged OS (11.1 vs. 15.8 months; p=0.075). These correlations were not seen in the reference cohort treated with SOC (PFS: 6.0 vs. 4.6 months; p=0.502; OS: 10.0 vs. 9.6 months; p=0.243). Conclusions: We show superior clinical efficacy of RT and NOX-A12 in patients with high frequency of CXCL12 expressing endothelial and glioma cells, suggesting the use of the EG12 score as a novel predictive biomarker for CXCL12-directed therapies in GBM. Clinical trial information: NCT04121455. Research Sponsor: TME Pharma AG.
Post-marketing surveillance safety analysis of patients with CNS malignancies treated with tumor treating fields (TTFields) therapy between 2011–2022.

Maciej M. Mrugala, Wenyin Shi, Fabio Iwamoto, Rimas Vincas Lukas, Joshua David Palmer, John H. Suh, Martin Glas; Department of Neurology and Hematology-Oncology, Mayo Clinic Cancer Center, Phoenix, AZ; Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, PA; Division of Neuro-Oncology, New York-Presbyterian/Columbia University Medical Center, New York, NY; Northwestern University, Chicago, IL; Department of Radiation Oncology, The James Cancer Hospital, Ohio State University Wexner Medical Center, Columbus, OH; Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; Division of Clinical Neuro-oncology, Department of Neurology, University Hospital Essen, University Duisburg-Essen, West German Cancer Center (WTZ) and German Cancer Consortium, Partner Site, Essen, Germany

Background: Glioblastoma (GBM) has a poor prognosis. Standard treatments are associated with systemic toxicity, further increasing the disease burden in this patient population. Tumor Treating Fields (TTFields) therapy was approved by the FDA for the treatment of newly diagnosed (nd) and recurrent (r) GBM based on the phase 3 EF-14 (TTFields therapy 200 kHz + temozolomide) and EF-11 (TTFields 200 kHz) studies, respectively. TTFields therapy is also approved for pleural mesothelioma. We report an updated global, post-marketing surveillance (PMS) safety analysis of patients with CNS malignancies treated with TTFields therapy over an 11-year timeframe. This analysis represents the largest dataset of TTFields therapy use to date. Methods: Unsolicited safety data were collected from routine post-marketing activities for patients (N = 25,898) in North America, Europe, Middle East and Africa and Japan, from October 2011 to March 2022. AEs were stratified by diagnosis, age, and sex and categorized using MedDRA version 25.1. Results: Diagnoses were ndGBM (68%), rGBM (26%), anaplastic astrocytoma/oligodendroglioma (4%) and other (2%). Baseline demographics were reflective of real-world practice: median (range) age was 59 (3–103) years; two-thirds of patients were male. Most (69%) patients were 18–65 years; 0.4% were < 18 years, and 30% were > 65 years. All-cause and TTFields-related AEs occurred in 18,798 (73%) and 14,599 (56%), patients, respectively. The most common device-related AE was skin reaction (43% patients overall). There were no major differences in occurrence of this AE between pediatric, adult, and elderly groups (39%, 42%, and 45%, respectively), or between males and females (41% and 46%, respectively). The incidence of device-related skin reactions was higher in ndGBM than rGBM (46% vs 34%, respectively), in line with previous reports. Only 405 (2%) of patients overall reported an AE of treatment-related ‘quality-of-life decreased’. In line with the phase 3 studies, there were no treatment-related systemic AEs. Conclusions: In this updated global PMS safety analysis, TTFields therapy demonstrated a tolerable safety profile in patients with CNS malignancies, with no new safety findings. In line with previous real-world and clinical data, most AEs were localized, non-serious skin events, which were consistent between age groups. Such events can typically be managed easily using prophylaxis and topical therapies, together with optimization of caregiver techniques. Importantly, no TTFields therapy-related systemic AEs were detected. Research Sponsor: Novocure Ltd.
Safety and efficacy of tumor treating fields (TTFields) prior and concomitant to radiotherapy in patients with newly diagnosed glioblastoma: Results from PriCoTTF.

Seid Kebir, Lazaros Lazaridis, Teresa Schmidt, Christoph Oster, Martin Proescholdt, Peter Hau, Anca L. Grosu, Dietmar Krex, Ulrich Sure, Björn Scheffler, Christoph Kleinschnitz, Christoph Pöttgen, Martin Stuschke, Martin Glas; Department of Neurology and Center for Translational Neuro- and Behavioral Sciences (C-TNBS), Division of Clinical Neurooncology, University Medicine Essen, University Duisburg-Essen, Essen, Germany; Department of Neurosurgery, University Hospital Regensburg, Regensburg, Germany; Department of Radiation Oncology, Medical Center - University of Freiburg, Freiburg, Germany; Department of Neurosurgery, Carl Gustav Carus University Hospital Dresden, Dresden, Germany; Department of Neurosurgery and Spine Surgery, University Medicine Essen, University Duisburg-Essen, Essen, Germany; DKFZ-Division Translational Neurooncology at the West German Cancer Center (WTZ), DKTK Partner Site, University Medicine Essen; German Cancer Consortium (DKTK), Germany; German Cancer Research Center (DKFZ), Heidelberg, Germany; Department of Neurology and Center for Translational Neuro- and Behavioral Sciences (CTNBS), Division of Clinical Neurooncology, University Medicine Essen, University Duisburg-Essen, Essen, Germany; Department of Radiotherapy, University Medicine Essen, University Duisburg-Essen, Essen, Germany; Department of Neurology and Center for Translational Neurooncology, University Medicine Essen, University Duisburg-Essen, Essen, Germany; Department of Neurology and Center for Translational Neurooncology, University Hospital Essen, University Duisburg-Essen, West German Cancer Center (WTZ) and German Cancer Consortium, Partner Site, Essen, Germany

Background: Tumor Treating Fields (TTFields) therapy is a locoregional, antimitotic cancer modality that utilizes electric fields delivered noninvasively to the tumor region using arrays. Preclinical findings have demonstrated that TTFields have an enhanced inhibitory effect on glioblastoma (GBM) cell proliferation when used concomitantly with radiotherapy (RT). These results provided the rationale for the phase 1/2 PriCoTTF study that investigated the safety and efficacy of TTFields therapy initiated prior and concomitant to radio-chemotherapy in adult patients with newly diagnosed (nd)GBM.

Methods: TTFields therapy was initiated following surgery and continued concomitant with radio-chemotherapy and adjuvant chemotherapy for a total of approximately 9 months. TTFields rechallenge was permitted upon GBM recurrence. RT was conducted with arrays placed on the patients’ scalp. The primary endpoint was safety and tolerability gauged by a series of pre-selected treatment-limiting toxicities (TLTs). Results: The baseline characteristics of 33 patients enrolled to date were typical for GBM, except for a small proportion of patients with gross total resection (22.5%). The frequency of adverse events (AEs) grade ≥ 3 was comparable to other studies in GBM. Of note, grade ≥ 3 skin AEs only occurred in 2 patients (6%) and no patients developed a TLT. The median duration of TTFields therapy was 8.4 months. Median overall survival (OS) was not reached (48% of events had occurred), which precluded conclusions regarding efficacy. However, notably, multivariable Cox regression found that OS was independently associated with the number of days patients achieved ≥ 23 h TTFields therapy (HR 0.96, 95% CI 0.93–0.99, P = 0.008). Conclusions: The PriCoTTF study met its primary endpoint by finding that TTFields therapy concomitant with RT was well tolerated in patients with ndGBM. This included that high-grade skin toxicities were rare. Longer follow up is needed to estimate the efficacy of TTFields therapy in this setting, and will need to consider the relatively low overall duration of TTFields therapy and proportion of patients who received GTR. Research Sponsor: Novocure Ltd.
A phase 0 pharmacokinetic trigger trial of infigratinib in patients with recurrent high-grade glioma.

Nader Sanai, Tigran Margaryan, Jennifer Molloy, Anita DeSantis, Jocelyn Harmon, Amy Hong, Kelly Braun, John Wanebo, Wonsuk Yoo, An-Chi Tien, Artak Tovmasyan, Shwetal Mehta; Ivy Brain Tumor Center, Phoenix, AZ; Barrow Neurological Institute (Phoenix, AZ), Phoenix, AZ

Background: This Phase 0 trial evaluates tumor pharmacokinetic (PK) and pharmacodynamic (PD) responses of fibroblast growth factor receptor (FGFR) inhibitor, infigratinib, in participants with recurrent high-grade glioma carrying FGFR1 K656E or FGFR3 K650E mutation or FGFR3-TACC3 translocation. Patients with high unbound drug concentrations in the gadolinium-nonenhancing tumor region were graduated to a therapeutic regimen of infigratinib. Methods: Recurrent high-grade glioma patients received 7 days of infigratinib (125 mg QD) prior to planned resection at 7-9 hours following the last dose. Tumor tissue (enhancing and nonenhancing regions), cerebrospinal fluid (CSF), and plasma were collected. Total and unbound infigratinib concentrations were measured using validated LC-MS/MS methods. A PK ‘trigger’ determined eligibility for the therapeutic expansion phase and was defined as unbound [infigratinib] > 5-fold biochemical IC50 (i.e., 5 nM) in non-enhancing tumor. PD response was assessed by quantification of percentage of positive pERK, MIB-1, and Cleaved Caspase 3 cells in the surgical tissue compared to baseline archival/biopsy tissue. Patients with tumors exceeding the PK threshold for unbound drug concentration were eligible for expansion phase therapeutic dosing of infigratinib. Results: Seven patients were enrolled into the Phase 0 study with 3 patients who met the PK threshold continued to the expansion phase. In non-enhancing tumor region, the mean unbound concentration of infigratinib was 3.5 nM (n=7). The mean non-enhancing tumor-to-plasma coefficient for unbound drug (Kp,uu) was calculated to be 1.4. The suppression of pERK levels and MIB-1 levels was observed in 17% (1/6) and 67% (4/6) of the patients, respectively. At a median follow-up of 16.3 months [range: 2.8-18.7 months], the median progression-free survival (PFS) was 2.8 months (n=3). One patient remains on treatment. No grade 3+ toxicities were observed, and no adverse events resulted in discontinuation of therapy. Conclusions: Despite relatively high unbound tumor-to-plasma (Kp,uu) value, infigratinib achieves sub-optimal unbound drug concentration in the non-enhancing brain tumor tissue. Pharmacodynamic response with archival tissue as comparator did not reveal inhibition of pERK. Clinical trial information: NCT04424966. Research Sponsor: The Ben and Catherine Ivy Foundation and Barrow Neurological Foundation.
H3.3-K27M neoantigen vaccine elicits anti-tumor T cell immunity against diffuse intrinsic pontine glioma: The phase I ENACTING trial.

Yang Zhang, Nan Ji, Gang Chen, Haiyang Wu, Yi Wang, Xiao’ou Li, Ling Peng, Wei Xu, Tian Li, Yi Wang, Li-Feng Zhang, Shengjun Sun, Xiaobin Zhao, Si Li, Frank Su, Qi-Jing Li, Liwei Zhang; Beijing Tiantan Hospital, Capital Medical University, Beijing, China; Biomedical Analysis Center, Chongqing, China; Guangdong TCRCure Biopharma Technology Co., Ltd, Guangzhou, China; Department of Neurosurgery, Beijing Tiantan Hospital, Beijing, China; Neuroimaging Center, Beijing Tiantan Hospital, Beijing, China; TCRCure Biopharma Corp., Los Angeles, CA, CA; Institute of Molecular and Cell biology & Singapore Immunology Network, Agency for Science, Technology and Research (A*STAR), Singapore, Singapore

**Background:** Diffuse intrinsic pontine glioma (DIPG) harboring H3.3-K27M mutation is a malignant pediatric brain tumor with a >90% mortality rate within two-year of diagnosis. Current therapeutic options for DIPG are limited. Aiming to improve therapeutic outcomes, we herein report the preliminary findings of a phase I trial studying a neoantigen peptide vaccine targeting H3.3-K27M. **Methods:** ENACTING is an open-label, single center, two-armed phase 1 trial to assess the safety and T cell immunity of a neoantigen peptide vaccine against H3.3-K27M. Patients aged ≥ 5 years old with newly diagnosed DIPG were consented and screened. HLA-A*02+/H3.3-K27M+ patients were enrolled to a two-arm study: Arm A consists of subjects receiving open debulking surgery, and Arm B consists of subjects without surgery eligibilities who received stereotactic biopsy. All patients subsequently received conformal radiotherapy and neoantigen vaccine treatment designed to elicit both CD4+ and CD8+ T cell immune response. Vaccine was administered intramuscularly in combination with polyinosinic-polycytidylic acid-poly-L-lysine carboxymethylcellulose (Poly-ICLC). The primary objective is to evaluate the safety (AEs graded by CTCAE v4.03) and survival outcomes. Secondary objectives include maximum tolerated dose (MTD) and immunological responses. **Results:** As of Jan 2023, 11 patients have been treated, with 7 in Arm A and 4 in Arm B. No grade 3-4 treatment-related adverse events have been observed, with fever (81.9%) and injection site pain (54.5%) being the most common AEs. Among 10 efficacy-assessable patients, median progression-free survival (mPFS) and median overall survival (mOS) were 11.4 months (95% CI: 5.8–14.7) and 15.4 months (95% CI: 7.53–not reached), respectively. One-year OS rate was 66.7% (95% CI: 42–100%). One patient was assessed as complete response (CR). T cell responses against neoantigen were detected and H3.3-K27M mutation-specific CD4+ and CD8+ TCR clones were validated. **Conclusions:** The H3.3-K27M neoantigen vaccine was well tolerated. Initial results from this ongoing study suggest that, compared with other current therapies against DIPG, H3.3-K27M peptide vaccination may provide superior patient survival outcomes. Clinical trial information: NCT04749641. Research Sponsor: Guangdong TCRCure Biopharma Technology Co., Ltd, Guangzhou, China.

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<td>Partial response</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>100%</td>
</tr>
<tr>
<td>12-month overall survival</td>
<td>66.7% (95% CI: 42–100%)</td>
</tr>
<tr>
<td>Median progression-free survival</td>
<td>11.4 months (95% CI: 5.8–14.7)</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>15.4 months (95% CI: 7.53–NR)</td>
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</tbody>
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Phase 1 study of pritumumab in brain cancer.

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Background: Pritumumab, a fully human IgG1 (kappa) monoclonal antibody (mAb), was originally isolated from a patient with cervical carcinoma. This classical example of a natural human anti-cancer antibody recognizes an altered form of the cytoskeletal protein vimentin, referred to as ectodomain vimentin (EDV). EDV is an ideal target for immunotherapy as it is expressed on the surface of tumor cells and is significantly overexpressed in glioblastomas (GBM). A multi-center phase 1 study was performed to assess the safety and pharmacokinetics of Pritumumab (NCT04396717). Methods: Eligible patients included age $\geq 18$ years, histologically confirmed diagnosis of a central nervous system cancer, and have failed prior standard therapy. Exclusion criteria included insufficient time from prior therapy characterized as less than 28 days from cytotoxic therapy, less than 14 days from non-cytotoxic investigational agent, and less than 7 days for non-cytotoxic or immunotherapy agent. Dose Escalation Schema: Five cohort arms with up to 6 patients at each dose level included Cohort 1 (1.6 mg/kg), Cohort 2 (4.8 mg/kg), Cohort 3 (8.0 mg/kg), Cohort 4 (12.0 mg/kg), and Cohort 5 (16.2 mg/kg) on weekly 3+3 dosing schedule. Dose escalation was based on the dose-limiting toxicities (DLT) encountered through Day 28 of treatment. Pharmacokinetics: Blood and CSF samples were collected for pharmacokinetic (PK) analysis both pre- and post-dose. Results: 24 patients provided informed consent and 9 were excluded for not meeting eligibility. 15 patients received the investigational agent and were evaluable for safety and efficacy analyses. 12/15 patients had a diagnosis of glioblastoma and one patient each had anaplastic astrocytoma, oligodendroglioma, and non-small lung cancer with brain metastases. 13 patients discontinued treatment due to disease progression, one due to PI discretion for an unrelated CNS infection, and one withdrew for personal reasons. One partial response showed nearly a 98.0% and 40.8% reduction in 2 tumor lesions for 17 months on study. There were no dose-limiting toxicities to this natural human IgG mAb. The most common adverse events at least possibly attributed to Pritumumab were fatigue (53.3%) and constipation (33.3%). Other rare side effects, possibly related to Pritumumab, occurred at 6.7% were nausea, joint tenderness, dehydration, hypomagnesemia, neuropathy, pruritus, scalp dryness, dry skin (face), and depression. There were no Grade 3, 4, or 5 adverse events attributed to pritumumab. Preliminary pharmacokinetic (PK) data shows volume of distribution as 38.36 mL/kg and clearance of Pritumumab as 0.1305 mL/h/kg. The half-life of Pritumumab was found to be 12.5 days. Conclusions: Single agent Pritumumab is safe up to a dose of 16.2 mg/kg every 7 days in brain tumor patients. A phase 2 study is being planned as single agent and in combination with checkpoint inhibitors in both recurrent gliomas and upfront with chemoradiation in newly diagnosed gliomas. Clinical trial information: NCT04396717. Research Sponsor: Nascent Biotech, Inc.
Zotiraciclib (TG02) for newly diagnosed glioblastoma in the elderly or for recurrent glioblastoma: The EORTC 1608 STEAM trial.

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Background: Zotiraciclib (TG02) is an oral multi-cyclin dependent kinase (CDK) inhibitor, including CDK-9, that inhibits tumor growth down-stream via depletion of survival proteins such as MCL-1 and MYC. MCL-1 and MYC are frequently overexpressed in glioblastoma. Methods: The EORTC 1608 (NCT03224104) (STEAM) phase 1b trial had a three parallel group (A,B,C) open-label, non-randomized, multicenter design. Groups A and B explored the maximum tolerated dose (MTD) of zotiraciclib in elderly patients (more than 65 years) with IDH1 R132H-non-mutant newly diagnosed glioblastoma or anaplastic astrocytoma, in combination with hypofractionated radiotherapy alone (group A) or temozolomide alone (group B), based on O6-methylguanine DNA methyltransferase promoter methylation status determined centrally. Group C explored single agent activity of zotiraciclib in IDH1 R132H-non-mutant glioblastoma or anaplastic astrocytoma at first relapse after temozolomide chemoradiotherapy with a primary endpoint of progression-free survival at 6 months. Secondary objectives included efficacy, quality of life, and safety. Results: The MTD was 150 mg in combination with radiotherapy alone (group A, n=12) or temozolomide alone (group B, n=9) in elderly patients. Two dose-limiting toxicities were observed at 150 mg, one in group A (grade 3 seizure) and one in group B (multiple grade 1 events). Main toxicities included neutropenia, gastro-intestinal disorders, and hepatotoxicity. Progression-free survival at 6 months in group C (n=50) was 6.7%. Conclusions: Zotiraciclib exhibits overlapping toxicity with alkylating agents and low clinical activity as a single agent. Larger randomized trials may be required to explore activity in combination with radiotherapy or temozolomide. Clinical trial information: NCT03224104. Research Sponsor: Cothera.
New ESMO scale for clinical actionability of molecular targets (ESCAT) for gliomas based on a multicentric real world data cohort using next-generation sequencing (NGS).

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Background: The ESMO ESCAT scale rank molecular alterations (MA) based on the published evidence supporting their clinical use. Building on our proposal for the first ESCAT classification for primary brain tumors (pBT) [Mirallas et al. ESMO 2022], we aim to describe the clinical actionability of NGS in a multicentric glioma cohort and gather clinical factors that enrich patients with MA to justify performing NGS. Methods: A multicentric retrospective study included pts with molecular profiling using NGS methods (Foundation Medicine, local NGS, Caris, Oncomine, and fusion panels). Clinical actionability was classified using the ESCAT scale; Tier 1 (ready for clinical implementation), Tier 2 (alteration-drug match with antitumor activity), Tier 3 (supported in other tumor types), and Tier 4 (preclinical evidence). Clinical factors considered for enrichment were diagnosis of glioblastoma (GBM), sex, and age ≤40 years, differences between groups were determined using Chi-squared test. The overall survival (OS) was calculated through Kaplan-Meier method and cox hazard ratio were fitted. Results: A total of 361 pts with NGS performed between Feb 2018 and Dec 2022 at 4 hospitals in Spain. Median age was 51.5 (range, 3.3-83.8), 77% had ECOG ≥1, 39.2% were women, 23.4% were 40 or younger, 20.8% had IDH1mut, and 73.5% had a diagnosis of GBM. The distribution of MA according to ESCAT was: 10 pts ESCAT 1 (5 BRAFV600E mut, 5 NTRK 1-3 fusions); 75 pts ESCAT 2 (67 IDH1 mut, 6 FGFR-TACC rearrangement, 4 FGFR 1-3 mut, 3 IDH2 mut); 105 pts ESCAT 3 (98 PIK3CA/PTEN mut, 12 PTEN loss, 11 H3K27M mut, 6 BRAF fusion, 2 MET mut, 1 FGFR3 amplification); 93 pts ESCAT 4 (119 TERT mut, 77 EGFR gain, 67 CDKN2A loss, 58 CDKN2B loss, 48 EGFRvIII rearrangement, 46 ATRX mut, 40 EGFR mut, 8 ATM mut). Prevalence of Tier 1-2 MA was 23.6%. In relation to enrichment factors: 12% of pts with GBM had ESCAT1-2 vs 61% in ≤40y (p<0.001), and non-gender differences were seen. The median OS for Tier 1-2 was 135 months (95% CI 166-99) vs Tier 3-4 of 24 months (95% CI 21.5-29.6). Significantly worse OS was observed for Tier 3-4 gliomas (HR: 4.11; 2.84-5.95, p<0.001), and remained significant after adjusting for histology and hospital center (p<0.01). Conclusions: The prevalence of ESCAT Tier 1-2 alterations is high in gliomas suggesting that molecular profiling should be offered, at least, in tertiary centers where these techniques are available. Potential enrichment factors to offer NGS were age and non-GBM pBT, but not gender. Research Sponsor: VHIO.
Distinct molecular features and potential therapeutic strategies for spinal cord gliomas.

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Background: Spinal cord gliomas (SCG) are rare primary CNS tumors with varied prognosis. Standard treatment remains poorly defined, as no clear survival advantage exists with extensive resection, radiation, or chemotherapy. Mounting evidence suggests that tumors from different regions of the CNS harbor unique molecular signatures. In a retrospective study, we comprehensively characterized molecular alterations to identify potential therapeutic strategies in the largest cohort of SCG reported to date.

Methods: We performed centralized pathology review and analyzed SCG with next-generation sequencing of DNA (592 gene NextSeq or WES, Novaseq), RNA (WTS, NovaSeq) and pyrosequencing (MGMT promoter methylation, MGMTme). We estimated tumor microenvironment cell infiltration by quantTIseq & Epithelial-Mesenchymal Transition (EMT) by RNAseq. We used X2/Fisher’s-exact/Mann-Whitney U tests for comparison & determined significance (p < 0.05), adjusting for multiple comparison by the Benjamini-Hochberg method (q < 0.05).

Results: We analyzed 39 surgically accessible SCG (19 high grade, 17 low grade, 3 NOS); ependymomas were excluded. The most common alterations were mutations in H3F3A (31%), TP53 (25%), ATRX (21%), NF1 (18%) & BRAF fusion (19%). H3F3A mutations occurred exclusively in high grade SCG (63%, q < 0.05) while BRAF fusions occurred exclusively in low grade SCG (60%, p < 0.05). TP53 mutations were more prevalent in high grade SCG (50% vs. 8%, p < 0.05). Compared to intracranial gliomas (n = 6732), SCG harbor significantly more frequent H3F3A (31% vs. 1.6%), KRAS mutations (10% vs. 0.7%) & BRAF fusions (19% vs. 0.7%) but less frequent TERT (4.3% vs. 66%) & PTEN (0 vs. 27%) mutations or EGFR amplification (0 vs. 28%) (all q < 0.05). SCG rarely harbor the canonical intracranial alterations IDH1 (2.6% vs. 17%), EGFRvIII (0 vs. 17%) or MGMTme (19% vs. 47%) (p < 0.05). SCG have greater penetration of immune infiltrates of DCs (median cell fraction/MCF: 13% vs. 9%), T regs (positive percent: 47% vs. 26%) & B cells (MCF: 9% vs. 7%), with less penetration of monocytes (MCF: 0 vs. 2%) (q < 0.05). EMT score associates with high grade glioma in intracranial disease (q < 0.05) but does not recapitulate in SCG (p > 0.05). Conclusions: Clinical management of SCG is currently drawn from experience with intracranial gliomas. Our results identify unique molecular features of SCG suggesting an underlying biology distinct from intracranial gliomas. In SCG, H3F3A mutations are exclusive to high grade while BRAF fusions are exclusive to low grade; SCG rarely harbor canonical intracranial alterations such as IDH1, EGFR or MGMTme; and SCG have greater penetration of DCs with less penetration of monocytes. We provide a biological explanation for limited effectiveness of current therapies in SCG with potential implications for chemotherapy, targeted and immunotherapy. Our work underscores the need for investigations dedicated uniquely to SCG. Research Sponsor: U.S. National Institutes of Health.
Prospective phase I study of checkpoint blockade for the treatment of patients with newly diagnosed high-grade glioma prior to radiochemotherapy: Results of nivolumab plus ipilimumab treatment arm.

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Background: The limited success of checkpoint inhibitors (CPI) targeting the programmed death-1 (PD-1) axis in the adjuvant setting for glioblastoma has prompted a deeper understanding of the brain tumor and immune microenvironment and evaluating how the sequence of immunotherapy administration impacts antitumor response. We initiated a feasibility study (NCT03425292) of postoperative nivolumab (anti-PD-1) monotherapy and combination therapy in adults with newly diagnosed high-grade gliomas (HGG) prior to radiotherapy.

Methods: Within six weeks from surgical resection of newly diagnosed HGG, patients in study Arm 3 received nivolumab 300 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks until disease progression or unacceptable toxicity. The primary endpoint was the rate of dose-limiting toxicities (DLT). Secondary objectives included adverse events, antitumor activity and pharmacodynamic effects of study treatment. Next-generation sequencing (NGS) was performed on archival tumor specimens before treatment and at the time of subsequent surgery. Results: Fifteen patients were treated with nivolumab plus ipilimumab. 27% (4/15) of patients were receiving dexamethasone at treatment initiation. MGMT promoter was methylated in 5 tumors, unmethylated in 9, and equivocal in one. The most common treatment-related adverse events (AEs) were rash, pruritus, fatigue, nausea, and anorexia. Grade 3 AEs were lipase increased (n = 2), anorexia (n = 1), pruritus (n = 1), and rash (n = 3), and Grade 4 cerebral edema occurred in 1 patient. Median progression-free survival (mPFS) was 1.3 months and median overall survival (mOS) was 19.3 months. Paired tumor specimens obtained before and after treatment were analyzed in six patients and revealed molecular changes in response to treatment as well as differences between patients with shrinking tumors versus progressing tumors. Conclusions: We show that nivolumab plus ipilimumab can be safely administered prior to radiation. To our knowledge, this is the first study in which checkpoint blockade therapy was administered for newly diagnosed glioblastoma prior to standard radiotherapy. Despite the short mPFS, mOS was suggestive of a potential long-term benefit from early CPI exposure, and three patients deferred chemoradiation greater than seven months. Analysis of other study arms is ongoing.

Clinical trial information: NCT03425292. Research Sponsor: PHASE ONE – The Road to Curing Cancer; Glen Turner, Jamie Siminoff.
Lisavanbulin (BAL101553), a novel, oral microtubule destabilizer plus radiation in patients with newly diagnosed, MGMT promoter unmethylated glioblastoma: A phase 1 Adult Brain Tumor Consortium study (ABTC1601).

Matthias Holdhoff, Xiaobu Ye, Roy E. Strowd, Louis B. Nabors, Tobias Walbert, Frank S. Lieberman, Stephen Joseph Bagley, John B. Fiveash, Joy D. Fisher, Serena Desideri, Marc Engelhardt, Thomas Kaindl, Heidi A Lane, Stuart A. Grossman, Lawrence Kleinberg; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Wake Forest University School of Medicine, Winston-Salem, NC; University of Alabama, Birmingham, AL; Henry Ford Hospital, Detroit, MI; University of Pittsburgh, Pittsburgh, PA; University of Pennsylvania, Philadelphia, PA; Basilea Pharmaceutica International Ltd, Allschwil, Switzerland

Background: Lisavanbulin (BAL101553, prodrug of BAL27862) is a novel, oral microtubule destabilizer that leads to cell death mediated by modulating the spindle assembly checkpoint. It has promising antitumoral activity in orthotopic glioblastoma (GBM) models in combination with radiation (RT) ± temozolomide (TMZ), including in MGMT promoter unmethylated (uMGMT) tumors. Lisavanbulin is a lipophilic and small molecule (MW 387), and data in rodents showed its ability to cross the blood-brain barrier (brain-plasma ratio 1:1).

Methods: This multicenter phase 1 study was to determine the MTD of oral Lisavanbulin in combination with standard RT (60 Gy in 30 fractions) in patients with newly diagnosed uMGMT GBM. Dose escalation followed a modified 3+3 design. The safety evaluation period ended 4 weeks after completion of radiation, which was also the end of study. Patients were allowed to continue treatment with standard adjuvant TMZ as per treating physician’s recommendation.

Results: Twenty-six patients with uMGMT GBM (median age 64y, 42.3% male, 61.5% with gross total resection, median KPS 80) were enrolled. Two GBM harbored an IDH1 mutation. Patients were treated at 5 different dose levels of Lisavanbulin administered once daily for 6 weeks concomitantly with RT: Lisavanbulin 4 mg (5 pts), 6 mg (5 pts), 8 mg (7 pts), 12 mg (5 pts), and 15 mg (4 pts). The initial starting dose was 8 mg. Due to Grade 4 aseptic meningoencephalitis in the first patient, the study was held and the dose decreased to 4 mg. Dose escalation resumed and continued to 15 mg with 1 DLT of Grade 2 confusion and memory impairment observed at 12 mg. A planned dose expansion was not conducted due to discontinuation of funding. Grade 3 AEs were hypertension (2), seizure (2), cognitive disturbance (1), cerebral edema (1), hyponatremia (1), and lymphopenia (1); no additional grade 4 AE was observed other than the 1 case of aseptic meningoencephalitis. Median OS was 12.8 months (95% CI: 9.1-18.3 months). At data cut-off, 8 subjects (30.8%) were still alive. 38.5% subjects had no information on disease progression and were censored during the estimation of PFS. The median PFS was 7.7 months (95%CI: 3.0-9.5 months).

Conclusions: The maximum studied safe dose for Lisavanbulin in combination with RT in newly diagnosed uMGMT GBM was determined at 15 mg daily during radiation. Overall, the safety of this combination was acceptable. Next steps in developing Lisavanbulin in newly diagnosed GBM include safety studies in combination with TMZ and of TMZ+RT in MGMT promoter methylated GBM prior to formally studying efficacy in a prospective randomized trial. Clinical trial information: NCT03250299. Research Sponsor: U.S. National Institutes of Health.
Real-world experience with tumor treating fields (TTFields) in newly diagnosed glioblastoma: A survival meta-analysis with systematic review.

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Background: Tumor Treating Fields (TTFields) are electric fields that exert forces on cancer cells, disrupting processes critical for cancer cell viability and tumor progression. TTFields therapy became an FDA-approved treatment option for patients with newly diagnosed glioblastoma (GBM) in 2015 on the basis of the randomized controlled EF-14 study (NCT00916409). Subsequent approvals worldwide and increased adoption of TTFields has led to the question of whether or not a consistent survival benefit has been observed in the real-world setting, and whether device usage has played a role.

Methods: A literature search was conducted using PubMed, Embase, and the Cochrane Library to identify clinical studies evaluating overall survival in adult patients with GBM treated with TTFields therapy. Comparative studies and single-cohort studies reporting on survival outcomes were included in the analysis. Inter-study heterogeneity was assessed using the Cochran Q test and quantified using the Higgins I^2 statistic. Survival curves were pooled using a distribution-free random-effects method.

Results: Our review identified 8 studies evaluating the clinical efficacy of TTFields therapy in newly diagnosed GBM, with patients spanning diverse geographic regions. Of these 8, 6 studies (reporting on a total of 1378 patients) compared the addition of TTFields therapy to standard of care (SOC) vs SOC alone, and were included in a pooled analysis for overall survival. Meta-analysis of comparative studies indicated a significant improvement in overall survival for patients treated with TTFields therapy vs those not receiving treatment (hazard ratio [HR]: 0.62; 95% CI, 0.52–0.73; P < 0.001). Inter-study heterogeneity was examined, and a sensitivity analysis indicated the pooled effect was robust and not dependent on any individual study. Among post-approval studies, the pooled median overall survival was 22.2 months (95% CI, 17.3–42.6) for TTFields-treated patients and 17.3 months (95% CI, 13.6–22.0) for the non-TTFields group. Rates of gross total resection were generally higher in the real-world setting, irrespective of TTFields use. Furthermore, among studies reporting data on TTFields device usage, an average device usage rate of 75% or higher was found to consistently associate with prolonged survival when compared to an average usage rate below 75% (pooled HR: 0.63; 95% CI, 0.48–0.83; P = 0.001).

Conclusions: Meta-analysis of comparative studies suggests a significant survival benefit with TTFields therapy added to standard radiochemotherapy for patients with newly diagnosed GBM, and that a 75% usage rate may be meaningful in the real-world setting. Research Sponsor: Novocure.
Safety and feasibility of JAK inhibitor ruxolitinib in newly-diagnosed high-grade gliomas (CRUX): Final toxicity report.

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Background: Dysregulation of the JAK/STAT pathway in newly-diagnosed high-grade gliomas (nHGG) is linked to enhanced survival and proliferation of tumor cells. Ruxolitinib, a small molecule inhibitor of JAK1, JAK2, and JAK3, limits glioma growth in preclinical models. This concept was explored in a phase I trial (NCT03514069), whose final report on toxicity is presented here. Methods: This non-randomized prospective study included 60 WHO Grade 3-4 nHGG patients who received standard of care (SOC) therapy along with ruxolitinib in a 3+3 dose-escalation design; level 1 of 10 mg BID, level 2 of 15 mg BID, level 3 of 20 mg BID, level -1 of 5 mg BID. The primary study objective was the determination of the maximum tolerated dose (MTD) of ruxolitinib in combination with chemoradiation. The secondary objective was the determination of safety, overall survival (OS), and progression-free survival (PFS). The exploratory aims were to investigate relationships between clinical outcomes and genomic signatures. Results: 60 patients were enrolled, with a median age of 60.5 years (range 22-78). 23 (38%) patients were female and 37 (62%) were male. 29 (48%) were MGMT unmethylated and received ruxolitinib with radiation of 60 Gy over 6 weeks. 31 (52%) patients were MGMT methylated and received ruxolitinib with 75 mg/m² of temozolomide (TMZ) with radiation of 60 Gy over 6 weeks. The 1-year OS rate was 77% for all GBM patients; 62% for arm 1 (unmethylated MGMT) and 93% for arm 2 (methylated MGMT). Median OS for arm 1 was 18.1 months (10.1, NA) and was not reached for arm 2. MTD for both cohorts was 20 mg BID. No dose-limiting toxicities were observed. Toxicities attributable to study medications included four grade 4 AEs including seizure, respiratory distress, somnolence, and thromboembolic event along with 14 grade 3 adverse events (AEs), including respiratory distress, seizure, gait disturbance, weakness, thrombocytopenia, cognitive disturbance, urinary retention, and meningitis. Conclusions: Ruxolitinib therapy is safe and feasible in combination with TMZ and radiation. Efficacy of ruxolitinib plus SOC appears promising compared to historical benchmarks for both MGMT methylated and MGMT unmethylated cohorts. A randomized phase 2 trial is planned. Clinical trial information: NCT03514069. Research Sponsor: Cleveland Clinic.
Phase I and pharmacodynamic study of arsenic trioxide plus radiotherapy for newly diagnosed glioblastoma.

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Background: Arsenic Trioxide (ATO) demonstrated prolonged survival in a transplanted rodent glioblastoma (GBM) model. Given the lack of effective therapies before temozolomide was available, the NCI funded NABTT Brain Tumor Consortium initiated a Phase I study of ATO with radiation in patients with newly diagnosed glioblastoma. Dose escalations using two different schedules of ATO were studied.

Methods: Patients with newly diagnosed GBM (MGMT and IDH mutation status unknown) were assigned to receive ATO once or twice weekly during the 6-week course of radiation. The starting ATO dose was 0.25 mg/kg. This was escalated by 0.05 mg/kg until an MTD was reached. Patients did not receive ATO or other adjuvant therapy once the radiation was completed. As ATO affected tumor vasculature and blood flow in experimental imaging studies, perfusion MRIs were obtained before ATO administration and one and six weeks later. Survival was a secondary endpoint.

Results: Thirty-one patients were enrolled: median age 54.9 years, 68% male, 77% patients KPS >90, 77% had tumor resection. The MTD was determined to be 0.4mg/kg on the weekly schedule and 0.3mg/kg on the biweekly schedule. ATO was well tolerated with 81% of patients completing the 6 weeks combined treatment. Major dose limiting toxicities were increased aspartate and alanine aminotransferases and one case of hyperkalemia. For all patients the median overall survival (mOS) was 17.7 months and the median progression-free survival (mPFS) was 5.4 months. However, there was a significant survival difference between the two ATO dose schedules across all doses with a mOS of 22.8 months in the biweekly schedule, vs 12.1 months in the weekly schedule (P = 0.039). There was a similar difference in mPFS (10.2 months vs 3.2 months, respectively, P = 0.004). Similarly, there were significant differences in perfusion imaging between the two ATO dose schedules with relative cerebral blood flow showing a significant decrease after one week of ATO treatment on the biweekly schedule (p = 0.007).

Conclusions: The MTDs of ATO in patients with GBM administered once or twice weekly for six weeks with standard radiation were determined. This regimen was well tolerated. Survival in patients on the biweekly schedule was much better (22.8 months) than expected in patients not receiving temozolomide. In addition, patients on biweekly ATO also had significant changes on MRI perfusion studies suggesting a pharmacodynamic effect of this agent. These finding should be explored further in patients with newly diagnosed MGMT unmethylated GBM where temozolomide has very limited activity. Clinical trial information: NCT00045565. Research Sponsor: U.S. National Institutes of Health.
Efficacy of function-enhanced, re-activatable, dual-specific CAR T cells pre-loaded with oncolytic virus for immunotherapy of high-grade glioma.

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Background: While cancer therapeutics have made tremendous progress within the past several decades, this benefit has not been seen in many primary cancers of the brain. Particularly confounding have been high-grade gliomas (HGG), which retain a dismal prognosis. Currently, novel therapies are being explored to rise to this unmet, critical need. One such therapy are CAR T cells, immune cells which have been engineered to target malignancy-specific antigens. Unfortunately, the efficacy of CAR T cell therapies against solid tumors is significantly limited, in large part due to impaired expansion/persistence in the immune suppressive tumor microenvironment (TME). Here we show that in vivo reactivation of CAR T cells through their native T Cell Receptor (TCR) by an oncolytic virus (OV) has therapeutic benefit in HGG. Methods: An EGFRvIII third-generation MSGV1 retroviral CAR construct containing the CD28, 4-1BB, and CD3z moieties, in tandem with the scFv derived from the human monoclonal antibody 139 and the marker Thy1.1 (38) was used to generate our CAR T cells. C57Bl/6 mice were used for in vivo experiments and both B16- and CT2A-EGFRvIII murine glioma cell lines were injected in the brain to model HGG. OVs and CAR T cells were given systemically by tail vein. OVs used include reovirus, vesicular stomatitis virus, and adenovirus. Results: By using OV in combination with EGFRvIII CAR T cells, we were able to generate a CD8 CAR population with TCR specificity for both the EGFRvIII and OV epitopes. These dual-specific (DS) CAR T expressed a memory phenotype and persisted for much longer than conventional CAR T cells. Further, we showed that these DS CAR T cells are more cytotoxic and can respond more rapidly than their conventional counterparts. We created a novel delivery mechanism for this combination OV + CAR T therapy using virus-loaded CAR T cells to bypass initial antiviral clearance from the immune system. Treatment with these OV-loaded CAR T cells lead to significant benefit in mice with HGG tumors which could be further enhanced by a systemic boost with OV, which rapidly re-activated DS CAR T cells against tumor and resulted in long-term cures of greater than 80% of treated animals. Conclusions: These promising results show that DS CAR T cells can overcome the critical therapeutic challenge of CAR T as a treatment for solid tumors. Given these promising results, we will go on to develop a clinical trial in which CAR T cells will be pre-loaded with OV and administered intravenously to patients with HGG, followed by systemic boosting with virus to re-activate DS CAR T cells against their tumor. Research Sponsor: Mayo Foundation; Mayo Clinic Ventures.
Background: Anti-angiogenic therapies, anti-VEGF agents, cause high radiographic response rates due to reduction in vascular permeability. However, we theorized the degree of tumor shrinkage combined with the duration of response might be a more meaningful measure of tumor control and may better reflect real patient benefit. In the current study, we investigate the association between model-derived parameters describing enhancing tumor volumetric dynamics and overall survival (OS) in recurrent glioblastoma treated with anti-VEGF therapy from multiple clinical trials. Methods: N=134 patients treated with bevacizumab +/- irinotecan (BRAIN Trial; NCT00345163) and N=121 patients treated with cabozantinib (XL184-201; NCT00704288) were used to identify potential imaging biomarkers, and N=63 patients in the bevacizumab control arm in a phase III trial (GLOBE Trial; NCT02511405) were used as a validation dataset. Enhancing tumor volumes were estimated using T1 subtraction maps, and a biexponential model was used to model tumor response (d) and regrowth (g) rates, as well as time to tumor regrowth (TTG), the inflection point where the tumor stops shrinking and starts to regrow, and the depth of response (DpR) after initiation of anti-VEGF therapy for each patient. Log-rank, univariate, and multivariable Cox regression were used to quantify the relationship of these parameters and OS. Results: Optimized thresholds based on maximum hazard ratio occurred at d=0.11 months⁻¹ (P=5x10⁻⁹ training; P=0.0082 validation); g=0.07 months⁻¹ (P=5x10⁻²⁰ training; P<0.0001 validation); TTG of 3.8 months (P=6x10⁻¹⁷ training; P<0.0001 validation); and DpR of 11.3% (P=0.0026 training; P=0.0177 validation). Univariate and multivariable Cox regression using these thresholds and controlling for age and baseline tumor volume confirmed that d, g, TTG, and DpR were all significant and independent predictors of OS in both phase II training and phase III validation datasets (P<0.01). Additionally, patients exhibiting combinations of a high DpR and/or long TTG showed differential median OS, while patients with favorable diffusion MR phenotypes exhibited a longer OS and significantly longer TTG. Conclusions: Volumetric response and regrowth rates, TTG, and DpR using a biexponential model are significant and independent predictors of OS in recurrent glioblastoma treated with anti-VEGF therapy. Clinical trial information: NCT00345163; NCT00704288; NCT02511405. Research Sponsor: U.S. National Institutes of Health.
Ultrasensitive detection and monitoring of central nervous system tumors from plasma using personalized whole-genome ctDNA profiling.

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Background: Patients with the central nervous system (CNS) tumors are largely followed up by imaging. Current plasma-based liquid biopsy techniques have limited utility in neuro-oncology due to a low circulating cell-free tumor DNA (ctDNA) burden, blood-brain barrier, and low number of mutations in coding regions. Whole genome sequencing (WGS)-derived patient specific mutational signature from a matched tumor-normal WGS can provide a personalized, highly sensitive and specific approach to detect mutations in ctDNA and provide blood-based monitoring in brain tumor patients. Furthermore, it can be performed on lower amount of peripheral blood since WGS requires less sequencing depth compared to targeted ctDNA panels.

Methods: We have profiled a cohort of 28 extra- and intra-axial adult and pediatric brain tumors including adult and pediatric low- and high-grade glioma (9), meningiomas (11), medulloblastomas (5), ependymomas (2), neurocytoma (1). Tumor DNA was extracted from archival pathology tissue, normal DNA from unsorted white blood cells, and ctDNA from 1-2 mL of post-surgery plasma. WGS was performed with 40x coverage for Tumor-Normal DNA and 20x for ctDNA. Using WGS of matched Tumor-Normal and plasma samples, we derived a personalized mutational pattern using SNVs, indels, and copy numbers for quantification and ultra-sensitive detection of ctDNA in plasma samples. An AI-based error suppression model was implemented to filter out the noise in the cell-free DNA (cfDNA) while the personalized mutational signature was used to detect the ctDNA in the cfDNA and to amplify the somatic signal to determine the Tumor Fraction at the time of diagnosis, during the therapy or surveillance period. The ctDNA Tumor Fraction (TF) was compared to the clinical status and MRI-based imaging.

Results: All subtypes of brain tumors contained enough mutations to derive personalized mutational signatures. Most mutations were distributed in the noncoding DNA. TF correlated with clinical status and with the disease course on imaging at given time points reaching a $10^{-4}$ minimal residual disease detection sensitivity. We were able to detect ctDNA across all WHO grades ranging from WHO 1 meningioma to WHO 4 glioblastoma and medulloblastoma. Furthermore, we were able to detect tumor-specific copy number aberrations such as MYCN amplification in plasma samples and mutational signatures.

Conclusions: Here we demonstrate that patient-specific WGS tumor signature in ctDNA from plasma can be used for sensitive monitoring of adults and children with primary low- and high-grade CNS tumors. Research Sponsor: Internal funding; C2i Genomics Inc.
Immune checkpoint inhibitor (ICI) therapy in glioblastoma: Institutional experience at the Massachusetts General Hospital (MGH).

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Background: Immune checkpoint inhibitors (ICI) have resulted in promising outcomes in systemic cancer but response in glioblastoma (GBM) has not met early expectations based on early clinical trial results. Conflicting data exists regarding the incidence of pseudoprogression after ICI in brain tumors. Here, we present our institutional experience of the radiographic response following ICI therapy in GBM both at initial diagnosis and recurrence. Methods: We retrospectively identified IDH-wildtype GBM (per 2021 WHO criteria) patients treated either at time of initial diagnosis or at recurrence with nivolumab, pembrolizumab, or durvalumab between 2015 and 2022 at MGH. Overall radiographic and clinical responses after initiation of ICI were assessed in both groups. Results: 56 pts (18 female, 38 male) were identified (average age 58.6). Eight (14.3%) patients had ICI-related non-hematological toxicities, including granulomatosis folliculitis, arthritis and myositis, headache, acneiform rash, transaminitis, and gastritis). Four (7.1%) of the eight patients had to discontinue treatment due to ICI-related severe toxicity (hepatitis and/or gastritis) and were not included in the final response assessment. Of the remaining 52 patients, none had evidence of pseudoprogression related to ICI. We did not identify any complete response (CR) or partial response (PR) secondary to ICI monotherapy. In the 13 patients treated at initial diagnosis, the following radiographic responses were seen: CR=0, PR=0, stable disease (SD)=5 (38.5%), and progressive disease (PD)=8 (61.5%). In the 39 patients treated at disease recurrence, the responses were: CR=0, PR=4 (10.3%), SD=10 (33.3%), PD=22 (56.4%). Noteworthy, all patients with PR were concurrently treated with bevacizumab. Conclusions: 0/52 patients showed radiographic response after ICI monotherapy. While treatment was overall tolerated, ICI therapy was discontinued due to toxicity in 7% of patients. Pseudoprogression attributable to ICI was not seen in any of the patients treated. Research Sponsor: None.
Vulnerability to immune therapy in BRAF- and MYB-altered pediatric gliomas.

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Background: The frequency and expression of predictive immune biomarkers in pediatric gliomas is relatively unknown. Here, we sought to define predictive signatures of immunotherapy responders by examining immune checkpoint expression, immune cell population signatures, and gene amplifications in a variety of pediatric gliomas. Methods: We profiled a cohort of pediatric, adolescent, and young adult glioma samples submitted to Caris Life Sciences (Phoenix, AZ) for analysis (N = 207). The cohort was further stratified by driver mutations: IDH mutant (N = 103), H3-3A mutant (N = 36), MYB-altered (N = 4), BRAF-altered (N = 39), and IDH wild type [IDH WT] (N = 25). De-identified next generation DNA sequencing (592-gene or whole exome) and RNA (whole transcriptome) sequencing were used to determine tumor-infiltrating immune cell signatures and immune checkpoint protein expression. Transcriptomic signatures predictive of response to immunotherapy (T cell inflamed score) and replication stress response defect (RSRD) score were calculated on transcripts per million (TPM) values. Immune cell fractions were estimated using RNA deconvolution (quanTIseq). Results: BRAF-altered tumors showed the highest IFN gamma signature (a clinically relevant inflammatory biomarker), a high pro-inflammatory M1 macrophage signature, and very high CD4+/CD8+ T cell signatures compared to other tumor groups. IDH mutant, but not WT gliomas, were relatively deficient in T cell infiltration but revealed an increase in dendritic cell signatures. IDH WT gliomas showed more T cell enrichment but higher immune suppressive checkpoint expression. H3-3A mutant tumors showed relatively low immune cell infiltration and immune checkpoint expression. Pro-inflammatory M1 macrophages were lower in the high-grade glioma microenvironment compared to low-grade. Immune suppressive M2 macrophages were elevated in the IDH WT microenvironment relative to other gliomas. There was no apparent difference in the frequency of PD-1+ T cells and tumor-expressed PD-L1 among the various molecularly defined pediatric glioma groups. Conclusions: In general, BRAF- and MYB-altered gliomas displayed high immune activation relative to other tumors. IDH WT tumors have an immune suppressive microenvironment with relatively high immune checkpoint expression. Based on predictive markers, BRAF- and MYB-driven gliomas show signatures suggesting the possibility of a greater response to immunotherapies than IDH WT/mutant gliomas or H3-3A gliomas. Research Sponsor: None.
Phase I study of BTK inhibitor ibrutinib with temozolomide and radiation in newly-diagnosed glioblastoma (EQUILIBRIUM): Final trial report.

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**Background:** Novel therapeutic strategies are urgently needed in newly-diagnosed glioblastoma (GBM). Ibrutinib, an oral small molecule inhibitor of BTK, is currently being investigated for several B-cell malignancies and solid tumors. Preclinical evidence suggests ibrutinib in inhibiting cancer stem cell in glioblastoma. We sought to investigate the safety and tolerability of ibrutinib in nGBM.

**Methods:** A non-randomized, prospective phase I trial was conducted in nGBM patients with Karnofsky performance status ≥70% and normal organ function, who received standard of care chemoradiation plus ibrutinib in a 3+3 dose-escalation design (level 1: 420 mg daily, level 2: 560 mg daily, level -1: 280 mg daily). Primary study objective was to determine maximum tolerated dose (MTD) of ibrutinib in combination with radiotherapy (RT) of 60 Gy over 6 weeks with/without 75 mg/m² of temozolomide (TMZ). Secondary objective was to determine safety, overall survival (OS), and progression-free survival.

**Results:** 26 patients were enrolled, with 12 (46%) females. Median age was 61.5 years (range 76-22). 15 (58%) patients were MGMT methylated and 11 (42%) were unmethylated. Dose-limiting toxicities (DLTs) were observed at all dose levels of ibrutinib plus RT (ibru+RT) cohort. MTD of ibrutinib was noted to be 420 mg daily with RT+TMZ. All MGMT methylated and 2 unmethylated patients received ibrutinib+RT+TMZ. Remaining 9 unmethylated received ibru+RT. In ibru+RT+TMZ, median cycles of TMZ were 4 (range 0-6) and of ibrutinib were 3 (range 0-26). EGFR amplification status was available for 22 patients, of which 8 (36%) were amplified. Survival outcomes are described, stratified using log-rank test.

**Conclusions:** 420 mg of Ibrutinib daily is safe and feasible in combination with TMZ and radiation in nGBM. Outcomes of ibrutinib appears promising compared to historical survival data in the MGMT methylated cohorts. Further trials are planned. Clinical trial information: NCT03535350.

**Research Sponsor:** None.

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<th>Group</th>
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<td>N (months: 95% CI)</td>
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<td>Overall</td>
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<td>MGMT Unmethylated</td>
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<td>Received Ibrutinib+RT</td>
<td>9 10.6 (8.54-NA)</td>
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<td>8 29.5 (21.9-NA)</td>
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<td>EGFR Non-Amplified</td>
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Interrogating drug action and immune response in organotypic glioma microenvironment.

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Background: The glioma tumor microenvironment is characteristic of a high level of heterogeneity and a profoundly immune suppressive phenotype as driven by the presence of glioma stem cells and abundant innate immune cells of the myeloid lineages, rendering glioblastomas (GBM) recalcitrant to conventional treatments and immunotherapies. To address the full complexity of the brain tumor with its diverse components, we have developed an organotypic slice culture system to overcome several limitations of the other preclinical models and allow interrogation of drug action and immunomodulatory agents in human GBM ex vivo. Methods: We performed extensive characterization of the organotypic glioma slice system and optimization of the ex vivo tissue culture conditions, and determined the longitudinal dynamics of slice cell viability, relative tumor versus immune cellularity, and responses to a selection of therapeutic agents and cytokines by multiplexed flow cytometry and single cell transcriptome (scRNA seq) profiling. Results: Single cell transcriptomic analysis showed that both tumor and immune cell heterogeneity were preserved ex vivo for the two-week observation time, which exhibited tumor-type specific gene expression profiles suggesting cooperative interactions among cell populations. Consistent with the findings in fresh tumor specimens and an immune suppressive microenvironment, we found a scarcity of T lymphocytes in IDH mutant gliomas, whereas abundant T cells were found in recurrent GBM slices that persisted ex vivo. Additional analyses revealed that T cell infiltration in GBM was associated with the mesenchymal-like molecular phenotype, which exhibited remarkable intratumor heterogeneity highlighting the presence of stem-like cells and a unique cell population expressing aberrant cancer genes and antigen presenting molecules. We further found that T cells in organotypic GBM slices acquired a potent effector phenotype in response to cytokine-induced reprogramming of microglia and tumor-associated macrophages. In addition, scRNA seq also revealed a population of cancer-associated fibroblast-like cells that are present in all tumors sequenced, which may function to mediate the interactions between immune and tumor cells as our data suggested. Conclusions: We demonstrated that the organotypic slice culture system we developed is compatible with genomic, pharmacological, and immunotherapeutic manipulations and provided data showing that organotypic slice culture preserves glioma microenvironment ex vivo allowing acquisition of crucial information of response of heterogeneous patient tumor tissue to the agent tested. This method represents a unique mechanism by which therapy development can be facilitated in an ex vivo setting. Research Sponsor: MD Anderson MoonShot Program.
A phase 0/2 trigger trial of niraparib in patients with newly diagnosed glioblastoma.

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Background: Poly (ADP-ribose) polymerase (PARP) mediates DNA damage response; niraparib is an investigational PARP1/2-selective inhibitor. This Phase 0 study evaluates newly-diagnosed glioblastoma (GBM) tumor pharmacokinetics (PK) and pharmacodynamics (PD), graduating patients with O6-methylguanine methyltransferase (MGMT) unmethylated tumors into a therapeutic regimen of niraparib plus fractionated radiotherapy when high unbound drug concentrations are present in gadolinium-nonenhancing tumor. Methods: Patients with presumed newly-diagnosed GBM were enrolled in a phase 0 study receiving 4 days of niraparib (300/200 mg QD) prior to planned resection 3-5 or 8-12 hours following the last dose. Tumor tissue (enhancing and non-enhancing regions), cerebrospinal fluid (CSF), and plasma were collected. Total and unbound niraparib concentrations were measured using validated LC-MS/MS methods. PARP inhibition was assessed by quantification of PAR induction after 10 Gy ex vivo irradiation in surgical tissue compared to non-irradiated control tissue. A PK ‘trigger’ determined eligibility for the therapeutic expansion phase and was defined as unbound [niraparib] > 5-fold biochemical IC50 (i.e., 19 nM) in non-enhancing tumor. Patients with MGMT unmethylated tumors exceeding this PK threshold were eligible for expansion phase dosing of niraparib plus radiotherapy followed by a maintenance phase of niraparib. Results: All patients (n=35) enrolled in the phase 0 portion of the study met the PK threshold. In non-enhancing tumor regions, the mean unbound concentration of niraparib was 253.2 nM in 32 evaluable GBM patients. The suppression of PAR levels after ex vivo radiation was observed in 75% of the patients (18/24). Eleven out of 18 patients with unmethylated tumors enrolled in phase 2. Five of the 6 initial patients enrolled in phase 2 experienced thrombocytopenia related to niraparib, and 3/5 cases were deemed serious and life-threatening. Consequently, starting dose in both phases was lowered to 200 mg, and no serious AEs were observed thereafter. At a median follow-up of 8.1 months (range: 6.0-12.9 months), PFS6 was 64% (n=11) with 4 patients remaining on treatment and 5 patients ongoing survival follow-up. Conclusions: Niraparib achieves pharmacologically-relevant concentrations in non-enhancing, newly-diagnosed GBM tissue in excess of any other studied PARP inhibitor. Clinical trial information: NCT05076513. Research Sponsor: The Ben and Catherine Ivy Foundation; Barrow Neurological Foundation.
Investigation of leptomeningeal disease in high grade glioma and characterization of molecular alterations.

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Background: Leptomeningeal disease (LMD) is a challenging complication of high grade glioma (HGG) and questions remain regarding risk factors, molecular associations, and optimal treatment. Here we report updated results on a larger cohort from our previously reported multicenter study (Shoaf 2022, Neuro-Oncology).

Methods: Patients with molecularly-profiled HGG (Caris Life Sciences; Phoenix, AZ) with LMD at 3 institutions were included. NextGen Sequencing of DNA (592 gene or whole exome) and RNA (whole transcriptome) were tested. Medical records were reviewed for clinicopathologic characteristics and outcome. Kaplan-Meier estimates of survival were performed using Cox’s proportional hazards model. Mann-Whitney U or Chi-square tests were applied for molecular comparison as appropriate and adjusted for multiple comparisons.

Results: Seventy-two patients (female: 20, male: 52; median age: 54.5y) were identified, comprising 65 grade 4 tumors (glioblastoma [GBM]: 62; gliosarcoma: 2; H3K27M diffuse midline glioma: 1), 5 grade 3 tumors (astrocytoma: 4; pleomorphic xanthoastrocytoma: 1), and 1 astrocytoma NOS. LMD diagnosed at glioma diagnosis (n=23) vs. recurrence (n=44) was associated with longer post-LMD survival [pLMD-OS: 16.9m vs. 5.5m, p<0.0001] but similar overall survival [mOS: 16.9m vs. 20.9m; p=0.36]. Pathology-diagnosed LMD (n=15) vs. MRI-diagnosed LMD (n=54) was associated with longer post-LMD survival [pLMD-OS: 15.2m vs. 6.2m, p=0.0002] but similar overall survival [mOS: 16.9m vs. 20.9m; p=0.72]. Post-LMD survival [pLMD-OS: 8.7m vs. 6.8m, p=0.33] and overall survival [mOS: 21.1m vs. 20.9m, p=0.20] were similar for supratentorial (n=45) vs. infratentorial/spinal (n=10) locations, and post-LMD survival did not significantly differ for symptomatic (n=40) vs. asymptomatic (n=22) patients [pLMD-OS: 6.6m vs. 10.5m, p=0.13]. pTERT mutation (73%), MGMT methylation (38%), EGFR amplification (31%), and PTEN mutation (28%) were the most prevalent molecular alterations in this group. Comparison of grade 4 LMD tumors with an independent GBM cohort (n=5431) suggested a male predominance (73.4% vs. 58.5%, p=0.016) and a trend towards more frequent mutations in RB1 (25% vs. 9.2%, p=0.002) and MDM4 (12.7% vs. 4.3%, p=0.01) and amplification of WIF1 (6.1% vs. 0.3%, p=0.006), CHIC2 (17.0% vs. 5.2%, p=0.002), and LGR5 (5.9% vs. 0.4%, p=0.012). The expression of immune checkpoint-related genes was similar, although a trend towards immunologically “colder” tumors in the LMD cohort was observed. However, these effects were not significant after correcting for multiple comparisons.

Conclusions: LMD is more common in male patients and may be associated with various genomic alterations and tumor microenvironment differences. Overall survival does not differ from patients without LMD, but these differences may provide clues to the pathogenesis and treatment resistance of GBM. Research Sponsor: None.
Intra-operative desorption-electrospray ionization mass-spectrometry for real-time diagnosis, margin assessment, and maximization of brain cancer resection.

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Background: Despite advances in our understanding of brain cancer, the ability to discern between infiltrated and non-infiltrated tissue with current adjuncts, remains elusive. Isocitrate dehydrogenase (IDH) mutation is unique to IDH-mut glioma cells and can be used as a surrogate for tumor infiltration. Further, emerging evidence has shown unique signatures in brain cancer lipidomic profiling, with lipid metabolism playing a key role in brain cancer biology. Here, we aimed to evaluate the impact of desorption electrospray ionization-mass spectrometry (DESI-MS) as a near real-time method to determine infiltration status and the use of DESI-MS to perform intra-operative histological diagnosis.

Methods: This is a prospective multi-institution cohort study using intra-operative DESI-MS on freshly obtained tumor samples to evaluate 2-hydroxyglutarate (2HG), with post-hoc validation by review by a board-certified neuropathologist. For tumor cell estimation and tissue diagnosis, high-throughput DESI-MS was used for rapid analysis of high-density arrays using lipidomic profiling. Analysis of the data was performed using a pre-written algorithm employing a combination of Python- and MATLAB-based custom software allowing results in less than a second per sample. Results: A total of 496 tumor biopsies from 72 patients have been analyzed. Earlier iterations focused on absolute quantitation of 2HG in 247 biopsies from 49 patients to determine IDH genotype yielding sensitivity, specificity, and accuracy values of 89, 100, and 94% for core biopsies (71). Improvement in accuracy was obtained with relative measurement of 2HG in comparison to glutamate allowing for detection of IDH-mut infiltration at the margin, resulting in 93% sensitivity, 100% specificity, and 98% accuracy with turnover times averaging 3 minutes in 183 biopsies from 23 patients. Margin assessment beyond the limits of neuro-navigation and surgeon assessment showed tumor infiltration in 88% of margin biopsies from IDH mutant tumors (30 of 34 biopsies) with 100% accuracy. Intra-operative tissue diagnosis was pursued in 66 unique tumor samples using DESI-MS lipidomic profiling, including samples of normal brain parenchyma, gliomas, meningiomas and pituitary adenomas, split into two microarray sets (36 and 40 samples). Using estimated principal components as input features, high accuracy ( > 90%; ROC AUCs ≥ 0.89) was obtained for supervised tissue classification using simple machine learning algorithms. Conclusions: We present a novel system for intra-operative evaluation of tumor infiltration at the margin in gliomas and for intra-operative tissue diagnosis of brain cancer. Our method identified tumor infiltration beyond the surgical margins and serves as a foundation for future uses employing DESI-MS to allow for molecularly guided surgery in IDH-mut gliomas. Research Sponsor: U.S. National Institutes of Health.
Intraoperative glioma characterization using time-resolved fluorescence spectroscopy.

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Background: Extent of surgical resection significantly improves progression-free and overall survival in glioma patients. Due to the infiltrative nature of gliomas, tumor margin detection is often difficult, and current intraoperative visualization methods are limited. Time-resolved fluorescence spectroscopy (TRFS) has the potential of differentiating glioma from normal brain tissue, thereby maximizing extent and safety of resection. Methods: Twenty-seven preoperative patients diagnosed with glioma met inclusion criteria for an IRB-approved study aimed to assess the accuracy of TRFS relative to tissue histopathology for differentiating glioma from normal cortex (NC), normal white matter (NWM), and white matter with edema (WME). A multi-channel TRFS system was developed for in vivo brain tissue and tumor characterization during glioma surgery. A custom-designed fiber optic probe was used to deliver ultrafast laser pulses to tissue regions of interest and collect fluorescence signals, with simultaneous registration to intraoperative neuronavigation. The fluorescence light was collected using a photomultiplier tube and digitized across six wavelength bands. Biopsies were taken at each measurement site for evaluation by a blinded neuropathologist to determine the accuracy of TRFS, which was calculated using parameters derived from the recorded fluorescence pulse and used to characterize tissue signatures. Results: During surgical resection of 27 patients, 162 TRFS measurements were collected in vivo followed by biopsy of the same tissue. Samples from brain tumors (39 low grade gliomas (LGG, WHO grade I to III), 35 high grade gliomas (HGG, WHO grade IV)) were compared with 47 samples of normal brain tissue (NC and NWM). The time-resolved system was able to differentiate LGG from normal tissue with 97% sensitivity and 93% specificity (93% PPV and 98% NPV). When all tumor grades were tested, the sensitivity dropped to 91% (96% PPV and 86% NPV), which we believe reflects the heterogeneity of HGG. HGG alone showed a sensitivity of 83% and specificity of 93% (91% PPV and 88% NPV). Normal cortex had the fastest decays across all wavelength bands among different tissue types, WME had longer decays compared to other tissue types at all wavelengths, and HGG had a variable but predictably different fluorescence decay pattern. Conclusions: TRFS is an intraoperative tool that can distinguish glioma from normal brain tissue and has the potential to maximize safe surgical resection. Research Sponsor: Cedars-Sinai Medical Center.
Detection of methylation-based prognostic signatures in liquid biopsy specimens from patients with meningiomas.

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Background: Detection of distinct epigenetic biomarkers in circulating cell-free DNA (cfDNA) of liquid biopsy (LB) specimens (e.g. blood) fosters opportunity for prognostication of central nervous system (CNS) tumors and has not been thoroughly explored in patients with meningiomas. Methods: We profiled the cfDNA methylome (EPIC array) in serum from patients with meningiomas (MNG; n = 93) and harnessed internal and external meningioma tissue methylome data with reported follow up (n = 77). To predict recurrence risk (RR), we consolidated a tissue cohort with at least 5 years of follow up and divided them into confirmed recurrence (CR; either reported progressive disease in post-surgical imaging, or additional resections following initial surgery) and confirmed no-recurrence (CNR: no confirmed disease progression w/in at least 5-years of follow-up). Then through application of an iterative process consisting of multiple tissue- and serum-based supervised analyses, we identified risk-specific methylation markers with potential for serum application. which, when inputted into a random forest algorithm allowed for segregation of both tumor tissue and liquid biopsy specimens according to recurrence risk. We estimated immune cell composition using MethylCIBERSORT, where a reference methylome atlas of chosen immune cell types was utilized to deconvolute the MNG samples. Results: The resulting recurrence risk classifier demonstrated an appreciable predictive power in classifying samples as high or low recurrence risk across the tumor tissue cohort (ACC: 87.7%, CUI+: 86.4%). When compared to another classifier of rivaling purpose, our model demonstrated statistically significant agreement across primary meningioma samples (κ = 0.269, p = 0.01), and more accurately predicted samples to recur across expanded time windows (time to recurrence > 5 yrs). Across resulting liquid biopsy classifications, recurrence risk subgroups were analogous with reported risk factors, including WHO grade, extent of resection, and tumor location. Recurrence risk subgroups also demonstrated differential estimated immune cell contributions, with low-risk samples exhibiting a “hot” profile, or enrichment of B-Cells, CD56- and CD4 T-Cells, and natural killer cells. Notably, the estimated neutrophil to lymphocyte ratio, previously purported to be relevant to tumor prognosis, was appreciably higher for those meningioma samples with the highest recurrence risk. Conclusions: DNA methylation markers identified in the serum are suitable for the development of machine learning-based models which present high predictive power to prognosticate patients with meningioma and estimate a differential immune profile across recurrence risk groups. After validation in an external cohort, this noninvasive approach may improve the presurgical therapeutic management of patients with meningiomas. Research Sponsor: Hermelin Brain Tumor Center.
Background: Meningiomas account for nearly 1/3 of brain tumors and are characterized by a low mutational burden and dysregulation of DNA methylation. The promoter of FOXC1 is hypomethylated relative to dura in meningiomas of all grades and knockdown of FOXC1 in murine models causes craniofacial hypoplasia and absent frontal dura, suggesting a role as a meningeal identity gene. Here we perform a multi-omic analysis of FOXC1 expression in a large cohort of meningiomas.

Methods: A total of 555 meningiomas (148 grade I, 255 grade II and 87 grade III) were analyzed with next-generation DNA sequencing (592 gene NextSeq panel; n=150 or Agilent WES whole exome sequencing, n=405) and whole mRNA (WTS, NovaSeq, 555) at Caris Life Sciences (Phoenix, AZ). Top quartile transcripts per million (TPM) for FOXC1 expression were considered high (FOXC1-H) and bottom quartile low (FOXC1-L). Immune cell infiltration was estimated using RNA deconvolution by QuantiSeq to calculate median cell fractions (MCF) or positive percentages (PP). Data were analyzed using $X^2$/Fisher's exact/Mann-Whitney U tests. A p-value $<0.05$ after BH correction was considered significant.

Results: Median FOXC1 expression was 33 TPM. Expression of FOXC1 transcript was higher in lower grade tumors (I: 34, II: 29, III: 27, $q<0.05$). NF2 mutations were significantly more common in FOXC1-L than FOXC1-H tumors (45% vs. 68%, $q<0.05$). Although a higher percentage of FOXC1-H meningiomas harbored TERT promoter mutations (2% vs. 9%, $p<0.05$) and a higher percentage of FOXC1-L meningiomas harbored a TRAF7 mutation (19% vs. 5.5%, $p<0.05$), these differences were not significant after correction for multiple comparisons. Programmed cell death ligand1 (PD-L1/CD274, 2.27 vs. 492) and MHC-I (HLA-A: 58 vs. 109, HLA-B: 59 vs. 74, and HLA-C: 61 vs. 101) transcripts were more highly expressed in FOXC1-H than FOXC1-L tumors. FOXC1-L tumors exhibited significantly more B cells (MCF: 5% vs. 4%), M1 Macrophages (MCF: 2% vs. 1%), CD8+ T cells (PP: 27% vs. 7%), and a higher interferon gamma transcript signature than FOXC1-H. Infiltrates of NK cells (MCF: 3.5% vs. 4.3%) and dendritic cells (MCF: 6% vs. 8%) were higher in FOXC1-H (all $q<0.05$).

Conclusions: The craniofacial patterning transcription factor FOXC1 was found to be widely expressed in a large cohort of meningiomas and its expression is inversely correlated with WHO tumor grade. Multi-omic analysis reveals a significant relationship between FOXC1 transcript levels and key markers of the immune environment including PD-L1 transcript expression. These data suggest that FOXC1 is a marker of meningiomas in addition to its role as a meningeal identity marker during development. Functional studies are warranted to determine whether FOXC1 is necessary for meningioma growth, whether FOXC1 plays a direct immunomodulatory role in meningiomas, and whether the lower FOXC1 expression levels in high grade tumors represent a more embryonic phenotype. Research Sponsor: None.
3D volume growth rate evaluation in the EORTC-BTG-1320 clinical trial for recurrent WHO grade 2 and 3 meningiomas.

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Background: We previously reported that tumor 3D volume growth rate (3DVGR) classification could help in the assessment of drug activity in patients with meningioma (Graillon et al. 2021). This classification segregates meningioma response into three main classes and a total of five subclasses (class 1 = volume decrease ≥ 25%; 2A = tumor stabilization; 2B = 3DVGR severe slowdown; 3A and 3B = respective low and quick progression) based on the 3DVGR before and under treatment. The EORTC-BTG-1320 clinical trial was a randomized phase II trial evaluating the use of trabectedin for recurrent WHO 2 or 3 meningioma (Preusser et al. 2022). Objective: To evaluate the discriminative value of 3DVGR classification for response and clinical benefit prediction in the EORTC-BTG-1320 clinical trial. Methods: All patients with at least one available additional MRI before inclusion were included. 3D volume was evaluated on all consecutive MRI until progression. 3DVGR classification was applied on them as previously described. Clinical benefit was defined as neurological and/or functional status improvement and/or steroid decrease or discontinuation. Results: 17 patients were included in this post-hoc analysis with a median age of 58 years (range, 38-73). Treatments were trabectedin, bevacizumab, hydroxyurea or palliative care in 9, 3, 2 and 3 patients respectively. At first evaluation, 3DVGR classes were 1, 2A, 2B, 3A, 3B and not evaluable in 8%, 15%, 8%, 23%, 38% and 8%, respectively. Best 3DVGR classification was 1, 2A, 3A, 3B and not evaluable in 15%, 31%, 15%, 31% and 8%, respectively. 3DVGR did not differ by methylation subgroups and NF2 or CDKN2A alterations. All patients with progression-free survival longer than 6 months presented with best 3DVGR class 1 or 2. In contrast, all patients with PFS shorter than 6 months presented with best 3DVGR class 3 or not evaluable due to early progression. Median overall survival was 34.7 months for the entire cohort. 3DVGR classes 1 and 2 (combined) had a median overall survival of 34.7 months versus 7.2 months for class 3. Best objective response according to modified Macdonald response criteria were stable disease, progression or undetermined in 8, 6 and 3 patients respectively. Regarding the 8 stable patients, they were segregated into classes 1, 2, 3 or undetermined by the 3DVGR classification in 2, 4, 1 and 1 patients, respectively. Finally, all class 1 patients, 75% of class 2 patients and only 17% of class 3 patients presented with clinical benefit (neurological and/or functional status improvement and/or steroid decrease or discontinuation), respectively. Conclusions: Tumor 3DVGR classification may be helpful to discriminate early signal of treatment activity in an independent randomized phase II clinical trial. Clinical trial information: NCT02234050. Research Sponsor: PharmaMar, S.A.
The ketogenic diet plus standard of care for adults with recently diagnosed glioblastoma: Results from a phase 1 trial.

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Background: Facing limited treatment options, brain tumor patients are often highly motivated to use complementary therapies, including diet, to help themselves. There is now an abundance of preclinical evidence suggesting possible benefit with a ketogenic diet (KD) for brain tumor patients, but clinical evidence is still limited. Thus, we conducted a single-arm, phase 1 safety and feasibility trial of a KD among patients with recently diagnosed glioblastoma (GBM) during standard-of-care (SOC) treatment.

Methods: Adults with GBM within 3 months of diagnosis followed a supervised 16-week diet intervention of a standard 3:1 KD (Fat(g):Carbohydrate+Protein(g)) plus SOC chemoradiation. Primary outcome was safety, evaluated by weekly assessments of weight and body mass index (BMI). Secondary outcomes included feasibility (pre-specified as >50% of patients maintaining blood ketone levels >0.3 mM over 50% of study days), progression-free survival (PFS), overall survival (OS), health-related quality-of-life (QOL), and cognitive function. Twice daily blood glucose and ketone levels, weight/BMI, physical activity, and sleep were assessed by remote monitoring.

Results: Seventeen patients were evaluable: 53% women, median age 55, median Karnofsky Performance Status 85. All participants met the primary safety objective with no instances of excessive weight loss or related serious adverse events. Adherence to KD was high: all 17 patients maintained nutritional ketosis ($0.3 \text{ mM/dL} >50\%$ of study days, where 14 patients maintained nutritional ketosis $>85\%$ of study days. Median time to ketosis from diet initiation was 3 days. Diet-related AEs were mild and manageable; no patients came off study due to inability to tolerate KD. Median progression-free survival (PFS) and overall survival (OS) were 12.5 months and 28.6 months from KD initiation respectively. QOL, symptom control, and cognitive function remained stable or improved, although these did not reach statistical significance.

Conclusions: This phase 1 trial demonstrates that KD is safe and feasible for GBM patients receiving SOC, may improve outcomes, and provides a foundation for future randomized trials to assess efficacy.

Osmotic blood-brain barrier disruption with mannitol followed by methotrexate, rituximab, and carboplatin in treating patients with newly diagnosed primary central nervous system lymphoma.

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Background: Osmotic blood-brain barrier disruption (BBBD) uses intra-arterial (IA) mannitol to open the neuro-vascular unit to enhance delivery of therapeutic agents to the brain. We report the results of a multi-institutional, single arm, phase 2 study evaluating the efficacy and safety of BBBD-enhanced chemotherapy in combination with immunotherapy in patients with newly diagnosed primary central nervous system lymphoma (PCNSL). PCNSL is a rare non-Hodgkin’s lymphoma that is limited to the brain, cerebrospinal fluid, spinal cord and/or the vitreoretinal compartment. Methods: Non-immunocompromised subjects with newly diagnosed PCNSL received rituximab IV over 5 hours on day 1. On days 2 and 3, under general anesthesia in the angiography suite, subjects received IA mannitol immediately followed by IA methotrexate over 10 minutes, and then IA carboplatin over 10 minutes. Subjects received sodium thiosulfate IV for hearing protection at 4 and 8 hours after each carboplatin dose. Treatment was repeated every month for up to 12 courses in the absence of disease progression or unacceptable toxicity. Per institutional recommendations, further accrual was terminated during the COVID-19 pandemic. Contrast MRI was used for response assessment based on IPCG criteria. Results: Twenty subjects (10 F, 10 M, Median KPS = 80; range 40-100) received a median of 8 cycles at 3 US institutions. Sixteen radiographic complete responses (80%) and 1 partial response were documented, 3 subjects were not evaluable (2 withdrew consent and 1 unrelated death). Median PFS was 55.2 months (95% CI: 10.3 – not reached) and Median Overall survival was 82.8 months (95% CI: 19.8-145.8). Fourteen patients (82% of evaluable patients) had grade 3 or 4 adverse events (AE). Grade 4 AEs (n = 14 in n = 7 patients) included neurologic toxicities (ischemia, cervical cord inflammation, neuropathy) and blood/bone marrow toxicities (lymphopenia, neutropenia, granulocytopenia). There were no treatment-related deaths. Conclusions: We demonstrate the feasibility of performing BBBD in a multi-institutional setting with excellent PFS and OS in patients without whole brain radiation or autologous transplant. Our CR rates, PFS and OS are comparable to other IV high-dose MTX regimens, with acceptable toxicity profile and no documented treatment-related deaths. Clinical trial information: NCT00293475. Research Sponsor: U.S. National Institutes of Health; Jonathan D. Lewis Foundation and the Walter S. and Lucienne Driskill Foundation.
Belzutifan treatment of Von Hippel-Lindau (VHL) related central nervous system (CNS) hemangioblastomas (HBs): A single institution experience.

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Background: Patients with inactivating germline mutations in the VHL gene develop CNS (brain and/or spine) HBs and/or renal cancers, pheochromocytomas and pancreatic neuroendocrine tumors. The oral HIF2a inhibitor belzutifan has been approved by FDA for the treatment of VHL-related HBs. We present here data on a cohort of VHL patients with CNS HBs treated with belzutifan in a single institution.

Methods: Adult VHL patients, with radiologically documented CNS (brain and/or spine) HBs that displayed documented growth within the last 6 months prior to therapy, were treated with an initial dose of 120 mg belzutifan orally per day. Target lesions included HBs ≥0.4 cm long in one maximal cross-sectional diameter. Lesions were imaged by MRI at 1.5, 3, 6 months after initiation of treatment and at 6-month intervals thereafter. Solid enhancing lesions, associated cysts and peritumoral edema were recorded and quantified. Tumor sizes were evaluated by RECIST 1.1 criteria and volumetric analysis. All patients were evaluated and treated in the Hemangioblastoma Center and the VHL Clinic of the Massachusetts General Hospital Cancer Center. Results: At the time of analysis, 9 females and ten male VHL patients (n=19) have been treated. Median age at treatment initiation was 36 yo (range 19-59). Median follow up is 12 months (range 1-19.5 months). Two patients were not yet evaluable for response. Of 17 evaluable patients, 8 had a PR (ORR 47%; 95% CI, 34-60); 8 had SD and 1 patient had progression (PD, 5.8%). Two patients had dose reduction to 80 mg/d because of anemia. No patient had grade 3 or greater toxicity and no patient experienced a CNS related toxicity during treatment. Volumetric analysis of solid and cystic components of the lesions, VHL germline mutations and other correlates of response to belzutifan will be presented. Conclusions: Real world data collected at a single institution confirm the high response rate of both solid and cystic components of CNS HBs to the FDA approved HIF2a inhibitor, belzutifan. Belzutifan was well tolerated. Further prospective controlled studies addressing the optimal dose, schedule and duration of treatment of HBs with belzutifan are required. Research Sponsor: None.
MTHFR polymorphisms and neurotoxicity and overall survival after methotrexate-based therapy in primary CNS lymphoma.

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Background: The folate-antagonist methotrexate (HD-MTX) is an integral to induction chemotherapy for primary CNS lymphoma (PCNSL); however, it can be associated with toxicities, including injury to cerebral white matter known as leukoencephalopathy. Methylene tetrahydrofolate Reductase (MTHFR) is involved in intracellular folate metabolism, and MTHFR polymorphisms may affect CNS-specific side effects of HD-MTX. Here, we evaluated the possible association of MTHFR polymorphisms and HD-MTX-related CNS toxicity.

Methods: We retrospectively searched our institutional database at the Massachusetts General Hospital for newly diagnosed PCNSL patients treated with HD-MTX (without use of radiotherapy or intrathecal chemotherapy). MTHFR polymorphisms were correlated with evolution of leukoencephalopathy over a time period of five years and patient outcomes. ROC curves were generated to estimate the diagnostic ability of specific MTHFR genotypes. Survival was calculated using Kaplan-Meier survival analysis and log-rank test. The significance level was set at \( p \leq 0.05 \).

Results: Among 68 PCNSL patients, MTHFR polymorphisms were found in 60 individuals (88.2%; 677C>T: 29 patients, 1298A>C: 18 patients, combined 677C>T & 1298A>C: 13 patients). Neither MTX clearance nor disease response to HD-MTX was affected by specific genotypes, and complete response was achieved in 72.1% of patients by induction with HD-MTX-based therapy. However, the 1298A>C genotype was associated with increased frequency and severity of leukoencephalopathy over time \( (\chi^2 = 7.43) \). Such genotype predicted treatment-induced leukoencephalopathy with a sensitivity of 71.0% and a specificity of 62.2% (ROC: \( p = 0.019 \)). While progression-free survival did not differ in genotype-based subgroups, overall survival was significantly lower when the 1298A>C genotype was present.

Conclusions: The MTHFR 1298A>C genotype may serve to identify PCNSL patients at elevated risk for HD-MTX-induced leukoencephalopathy. This was associated with reduced overall survival, potentially due to decreased functional status in patients less suitable for aggressive subsequent therapies.

Research Sponsor: None.
The clinical relevance of margins in frameless stereotactic radiosurgery for intact brain metastases: A randomized trial of 0 vs 2 mm margins.

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**Background:** Stereotactic radiosurgery (SRS) is a commonly utilized treatment strategy for brain metastases which offers a relatively low rate of morbidity and high rate of local control. SRS delivers an ablative dose of radiation in a single session to a limited target volume while minimizing dose to surrounding normal tissue. Image-guided linear accelerator (LINAC)-based frameless SRS has enabled effective, safe delivery of high dose radiation without the discomfort and logistical complications associated with use of a rigid frame. Localization errors during frameless SRS vary depending on the specific LINAC configuration and immobilization technique. The clinical relevance of potential inaccuracies in localization with frameless SRS remains controversial. When employing frameless systems, many centers will account for set-up uncertainties by adding a circumferential margin of 1-3 mm around the GTV to create a planning target volume (PTV). This PTV expansion ensures adequate tumor coverage if target motion occurs, but exposes more normal brain tissue to radiation and may increase the risk of adverse events, chiefly radionecrosis. There is limited literature available to guide radiation oncologists on the appropriate choice of margin size, if any, for frameless SRS. There are no randomized data evaluating the safety and efficacy of omitting the margin entirely. Given the paucity of data examining margin extent and the potentially significant consequences for treatment efficacy and morbidity, we propose a phase II randomized prospective clinical trial evaluating 0 vs 2 mm marginal GTV to PTV expansions for treating patients with intact brain metastases with frameless SRS.

**Methods:** Eligible patients will have brain metastases from solid tumors with ECOG performance status of 0-2 and life expectancy of >3 months. Patients must have 1 - 5 newly diagnosed well-circumscribed, measurable intraparenchymal brain metastases with maximum tumor diameter ≤3.0 cm. At least one lesion must be ≥ 0.5 cm in maximum diameter to be considered measurable. SRS will be delivered in a single fraction to either 20 Gy or 18 Gy dependent on tumor size. Importantly, PTV margin randomization is blinded and occurs after delineation of tumor volume by radiation oncologist to not bias contouring based on knowledge of margin randomization. This is two-armed multi-center phase II randomized controlled trial. The trial is powered to demonstrate non-inferiority of the experimental arm with regard to the primary endpoint of local PFS at 6 months and the superiority of the experimental arm with regard to the secondary endpoint of radionecrosis or pseudoprogression. We expect the total study duration, from the start of screening for the first participant until the end of follow-up for the last one, to be approximately six years. We plan to accrue 166 patients to this trial at all sites. Clinical trial information: NCT02747303. Research Sponsor: None.
A phase 0/1a study of BI 907828 concentrations in brain tissue and a nonrandomized, open-label, dose escalation study of BI 907828 in combination with radiotherapy in patients with newly diagnosed glioblastoma (GBM).

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Background: Murine double minute 2 (MDM2) directly regulates the stability of the tumor suppressor p53, and dysregulation of this pathway can critically disrupt cellular response to genomic stress and lead to cell death. BI 907828 is a highly potent inhibitor of the MDM2-p53 interface that triggers accumulation of p53 and subsequent apoptosis in multiple GBM patient-derived xenografts (PDXs) with wild-type p53. Moreover, the combination of BI 907828 and radiotherapy provides significant survival extension in multiple orthotopic GBM PDXs. Methods: An integrated Phase 0/1 trial design is being used to evaluate the potential for BI 907828 to achieve a therapeutic concentration in brain tumor tissue and to test the safety of the combination with radiation. The co-primary endpoints for the Phase 0 study are i) measured total concentration of BI 907828 and ii) calculated unbound concentration of BI 907828 in contrast and non-contrast enhancing regions of tumor. Key inclusion criteria for the Phase 0 study are patients at least 18 years of age, ECOG performance status of 0 or 1, histologic or radiologic new diagnosis of GBM, and planned surgical resection. The first approximately 6 patients enrolled in the Phase 0 will be treated at the starting dose of 30 mg, and the future patients enrolled will be dosed at higher levels (45 mg or 60 mg) provided there are no safety concerns. If dose-limiting toxicities (DLTs) are encountered, then a Bayesian Logistic Regression Model (BLRM) with overdose control will be used to guide the dose level decisions for the additional patients. Multiple, image-registered tumor samples and intra-operative plasma samples will be analyzed for BI 907828 by LC-MS/MS. Intra-tumoral variation in BI 907828 will be correlated with pharmacodynamic effects of MDM2 inhibition (elevation of p53, p21, MDM2, GDF15, PUMA). Those patients completing the Phase 0 study and who meet additional eligibility criteria can enroll on the Phase 1a portion of the study. The pathologic inclusion criteria are TP53 wild-type, IDH1/2 wild-type, MGMT unmethylated GBM. Co-primary endpoints for the Phase 1a trial are i) occurrence of DLTs during and within 21 days after completion of radiation therapy, and ii) occurrence of adverse events throughout the treatment period. Tolerability of inter-patient dose-escalation of BI 907828 (30, 45, 60 mg) combined with radiation therapy (60 Gy in 30 fractions) will be evaluated with dose-escalation guided by a two-parameter BLRM with overdose control. Patients will remain on BI 907828 monotherapy following completion of radiotherapy until progression. To date, two patients have enrolled on the Phase 0 study, and one patient went on to enroll on the Phase 1a portion of the study. Clinical trial information: NCT05376800. Research Sponsor: Boehringer Ingelheim.
A first-in-human pharmacodynamic evaluation of dual polyamine depletion for patients with high-grade gliomas.

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Background: No drug has improved survival for patients with high-grade gliomas (HGGs) since temozolomide in 2005. Relatively little is known about the live response of in situ gliomas to therapeutic intervention. Phase 0 studies that leverage access to the live human glioma in situ, including via microdialysis to sample the live glioma microenvironment, provide an attractive and feasible solution to this problem. We performed intraoperative microdialysis to evaluate the extracellular metabolome of divergent regions in 15 HGG resections. Our data revealed a conserved metabolic signature of HGGs and a novel glioma-associated metabolite, guanidinoacetate (GAA). Pathways enriched in this tumor signature included methionine and polyamine metabolism. Although GAA is typically converted to creatine, we hypothesize that the high flux of ornithine through ornithine decarboxylase (ODC) results in excess GAA accumulation. As such, in a Phase 0 trial, we will evaluate in situ glioma responses to polyamine depletion via ODC inhibition (Difluoromethylornithine, DFMO), with or without blockade of polyamine uptake (AMXT 1501), to identify candidate extracellular biomarkers of target engagement and cytotoxicity. Methods: Patients will be recruited who are undergoing a clinically indicated subtotal resection for a known or suspected high-grade glioma (NCT05717153). At the end of the surgery, two microdialysis catheters will be implanted for postoperative microdialysis, one in residual tumor and one in brain adjacent to tumor for an internal control. Beginning on post-operative day (POD) 1, patients will be randomized to one of the following three groups, including administration of vehicle, DFMO (500 mg, PO, BID) and AMXT 1501 (600 mg, PO, BID): 1) DFMO + AMXT 1501 (POD1-5); 2) Vehicle (POD1–POD2), followed by DFMO + AMXT 1501 (POD3–POD5); 3) DFMO alone (POD1–POD2), followed by DFMO + AMXT 1501 (POD3–POD5). Throughout this time, extracellular metabolite levels of polyamines, guanidinoacetate, and glutamate will be quantified from microdialysate collected every two hours from intraoperatively implanted 100 kDA microdialysis catheters. The primary outcome of this study is to determine how polyamine depletion impacts extracellular intratumoral guanidinoacetate abundance. The secondary outcomes of this study are to (1) determine the impact of polyamine depletion on polyamine abundance and the global extracellular metabolome within live human gliomas, in situ, and (2) assess the feasibility of longitudinal microdialysis for pharmacodynamic analysis within live human gliomas in situ in the postoperative setting. Clinical trial information: NCT05717153. Research Sponsor: U.S. National Institutes of Health.
Phase 3 TRIDENT study (EF-32): Tumor treating fields (TTFields; 200 kHz) concomitant with chemoradiation, and maintenance TTFields therapy/temozolomide in newly diagnosed glioblastoma.

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Background: Tumor Treating Fields (TTFields) therapy, a noninvasive and locoregional antimitotic cancer treatment modality, is approved for newly diagnosed (nd), recurrent glioblastoma (r) GBM and mesothelioma. In patients with ndGBM, progression-free survival (PFS) and overall survival (OS) were significantly improved with TTFields therapy/temozolomide (TMZ) vs TMZ alone in the pivotal EF-14 study, leading to FDA approval in ndGBM. To avoid potential impedance of radiotherapy (RT), TTFields therapy was administered following RT/TMZ; however, preclinical studies have demonstrated that TTFields therapy enhances the therapeutic effect of RT. Methods: TRIDENT (EF-32; NCT04471844), a phase 3, global, randomized study, will evaluate TTFields therapy concomitant with RT/TMZ in patients ≥18 years of age (≥22 years in the US) with histologically-confirmed ndGBM, ≥3 months life expectancy, and ≥70 Karnofsky performance status. Patients will be stratified on the basis of MGMT promoter methylation status and extent of resections. Approximately 950 patients will be assigned 1:1 to continuous TTFields therapy (200 KHz, ≥18 h/day) concomitant with RT/TMZ (experimental arm) or RT/TMZ alone (control arm). Patients in the experimental arm will receive TTFields therapy continuously from the first day of chemoradiation. Patients in the control group will begin TTFields at the same time as maintenance TMZ, approximately one month after completion of chemoradiation. TTFields therapy will continue in both treatment groups until second disease progression (PFS2) or 24 months (if clinically able). The primary endpoint is median OS, and secondary endpoints include PFS, 1- and 2-year survival rates, objective response rate, PFS2, 6- and 12-month PFS rates, safety, and quality of life (EORTC QoL questionnaires). The ability of TTFields therapy to extend OS in a dose-dependent manner is an exploratory endpoint. The sample size is powered for a hazard ratio of < 0.8 with a 5% type I error. The hypothesis that first-line TTFields therapy/RT/TMZ can significantly improve OS vs RT/TMZ will be tested using a stratified log-rank test. The study is expected to enroll patients at 150 sites, with enrollment currently open in 9 countries. Clinical trial information: NCT04471844. Research Sponsor: Novocure.
Low-intensity focused ultrasound with systemic microbubble oscillators for blood-brain barrier disruption for liquid biopsy in glioblastoma (LIBERATE).

**Background:** Liquid biopsy in glioblastoma (GBM) is hindered by a lack of requisite circulating-free DNA (cfDNA) levels in blood due to the blood-brain barrier (BBB). This results in challenges to the identification of blood-based biomarkers and the development of novel biomarker-driven systemic therapies. Real-time image-guided low intensity focused ultrasound (LIFU) combined with IV microbubble oscillators (DEFINITY), non-invasively causes BBB disruption (BBBD). This clinical trial aims to evaluate the utility of LIFU for increasing cfDNA in blood for liquid biopsy in GBM.

**Methods:** LIBERATE is a prospective, multi-center, self-controlled, ongoing, pivotal trial evaluating safety and technical efficacy of LIFU for BBBD to increase cfDNA in blood for GBM. Patients aged >18-80 years with suspected GBM planned for tumor biopsy or resection at eleven centers in North America are being included. Patients with multifocal tumors or tumors arising from deep midline, thalamus, cerebellum, or brainstem are excluded. Patients are administered IV oscillating microbubbles for enhancing sonication, after which MR-guided BBBD using a 220 kHz LIFU device is performed with real-time acoustic feedback for effective cavitation. Before and after procedure, phlebotomies and MRI brain are performed to evaluate outcomes. The primary study endpoint is defined, per subject, as the ratio between their cfDNA level in blood 1-hour post-LIFU compared to cfDNA level in blood pre-procedure. The primary study hypothesis is that BBBD with LIFU leads to a 2-fold increase in cfDNA in blood. The secondary hypothesis is that there exists ≥75% agreement between biomarker pattern in cfDNA sample from 1-hour post-LIFU sample and biomarker pattern in tumor tissue obtained later. The trial has been powered to evaluate both primary and secondary hypotheses. Based on an assumed true agreement rate of 91% and a one-sided alpha of 0.025, an exact test for binomial proportions provides a sample of N=50 with 84% power for the secondary hypothesis. Exploratory endpoints include (1) sensitivity of detection of known somatic mutations in cfDNA from blood samples collected before and after LIFU, (2) estimation of cfDNA levels post-LIFU in samples collected at 30 minutes, 1 hour, 2 hour, and 3 hour to determine time of greatest yield, (3) correlation of MRI parameters related to grading of BBBD and biomarkers positive in cfDNA from post-LIFU blood samples.

Patient enrollment commenced in 2022 and 7 patients have been recruited by 02/13/2023. Clinical trial information: NCT05383872. Research Sponsor: Insightec.
Efficacy and safety study of neoadjuvant efineptakin alfa (NT-I7) and pembrolizumab in recurrent glioblastoma.

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Background: Glioblastoma (GBM) is the most common and aggressive form of brain tumor in adults. Despite maximal surgical resection, irradiation, and chemotherapy, median overall survival (OS) remains at only 30 weeks for recurrent GBM (rGBM) patients, emphasizing the need for novel treatments. GBM tumors are immunologically 'cold,' in that they have an immune-suppressive microenvironment with a low number of tumor-infiltrating lymphocytes (TIL). Interleukin 7 (IL-7) plays a key role in T cell development and survival. The physiological level of IL-7 increases to stimulate T cell expansion in lymphopenic condition. Previous studies have shown that lymphopenic GBM patients have shorter survival. However, their IL-7 levels are unexpectedly low. Efineptakin alfa (NT-I7), a long-acting IL-7, has been shown to increase effector CD8 T cells and reduce suppressor T-regulatory cells in murine GBM models, with subsequently improved OS. Further, we recently completed a Phase I study which showed that NT-I7 is safe, well-tolerated, and increased absolute lymphocyte counts (ALC) in newly diagnosed GBM patients. Phase II dosing was determined through this Phase I study reaching maximum tolerated dose. Thus, we hypothesized that NT-I7 may reverse GBM-associated immune suppression and potentiate the effect of an immune checkpoint inhibitor, leading to an increase in TILs and improved survival. Our preliminary data suggests that combining NT-I7 with pembrolizumab, an anti-PD-1 antibody, improves survival in murine glioma models. The purpose of this study is to evaluate the safety and efficacy of combining NT-I7 and pembrolizumab in rGBM patients. Methods: This is an open-label single arm one-stage Phase II study of NT-I7 and pembrolizumab as neoadjuvant and adjuvant therapy with surgery for adult patients with rGBM. We plan to enroll 30 evaluable patients, including a 6-patient safety run-in. Key eligibility criteria include candidates willing to undergo clinically indicated resection or biopsy, age ≥ 18 years, Karnofsky performance status ≥ 70, and dexamethasone dose > 2 mg/day ≤ 2 days prior to registration. The primary endpoint is a 9-month OS rate. Secondary endpoints include progression-free survival, objective response rate, changes in ALC, and adverse events profile. The correlative endpoints include studies to assess the anti-glioma immune response, changes in T cell subsets, T cell effector function, cytokine analysis, and immunohistochemical analysis of GBM tissue. Longitudinal cerebrospinal fluid proteomics is optional. This study opened on 1/20/2023. Two of the planned 30 patients had been enrolled by submission on 2/14/2023.

Clinical trial information: NCT05465954.

Research Sponsor: Supported in part by a research grant from Investigator-Initiated Studies Program of Merck Sharp & Dohme LLC.; The Ivy Foundation; Mayo Clinic Comprehensive Cancer Center; Humor to Fight the Tumor.
Phase 1b multicenter study to evaluate CHM 1101 in patients with recurrent or progressive glioblastoma.

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Background: Glioblastoma multiforme (GBM) is the most common and most aggressive primary brain tumor. More than 300,000 new cases are diagnosed globally with over 250,000 deaths each year (Sung H, et al. CA Cancer J Clin. 2021). Patients with recurrent GBM have a poor prognosis, with limited treatment options and a median survival of less than 1 year (Gallego. Curr Oncol, 2015). While prior attempts to treat GBM with chimeric antigen receptor (CAR) T-cells have been limited by tumor heterogeneity, chlorotoxin (CLTX)-directed CAR T-cells in mice demonstrated broad anti-tumor activity and prolonged survival with no off-tumor toxicity or antigen escape (Wang, et al. Sci Transl Med, 2020). CLTX, a 36-amino acid peptide identified in scorpion venom, selectively binds to malignant glioma cells through matrix metalloproteinase-2 (MMP2) and clinical administration of CLTX-based biologics has been well tolerated in patients (Mamelak, et al. J Clin Oncol, 2005, Patil, et al. Neurosurgery, 2019). CHM 1101 is the first CAR T to utilize CLTX as its tumor targeting domain for autologous CAR T-cell therapy. A single-center first-in-human phase 1 study of CHM 1101 in patients with recurrent GBM is ongoing. Methods: Clinical Trial NCT05627323 is a phase 1b, multi-center study of CHM 1101 in adult subjects with MMP2+ recurrent or progressive GBM after standard therapy. After leukapheresis and tumor resection, pts will receive CHM 1101 at Dose Level 1 ($240 \times 10^6$ CAR T cells) or Dose Level 2 ($440 \times 10^6$d CAR T-cells), divided across 3 once-weekly intracranial (intracavitary and intraventricular) administrations; after disease assessment at 28 days, additional doses of CHM 1101 can be administered on a weekly schedule. Eligible subjects have a prior histologically confirmed diagnosis of a grade 4 GBM, a grade 2 or 3 malignant glioma with radiographic progression consistent with a grade 4 GBM (IDH wild type), grade 4 diffuse astrocytoma (IDH mutant), or a unifocal relapse of GBM. MMP2+ tumor expression is confirmed by IHC ($\geq 20\%$ moderate/high MMP2 score [2+ or 3+]). The primary endpoint is safety; key secondary endpoints include feasibility, progression-free survival, overall survival, response rate (RANO criteria), and cellular kinetics. Recruitment is ongoing. Clinical trial information: NCT05627323. Research Sponsor: Chimeric Therapeutics.
Background: Diffuse gliomas are primary brain tumors characterized by substantial morbidity and mortality. Standard treatment includes maximal safe surgical resection followed by combination radiation and chemotherapy. Despite aggressive treatment, diffuse gliomas inevitably recur. Alkylating agents, and in particular temozolomide, play an important role in the treatment of gliomas, resulting in single-strand DNA breakages which require PARP activity for detection and repair. Gliomas with mutations in isocitrate dehydrogenase (IDH) 1 or 2 have an accumulation of 2-hydroxyglutarate (2HG) which results in a BRCA-like state of homologous recombination deficiency (HRD). When PARP is inhibited in the setting of HRD, single-strand DNA damage progresses to double-strand breaks resulting in synthetic lethality. PARP inhibition has also been shown to increase mutational burden and neoantigen expression ("immune-priming") and increases tumor-infiltrating lymphocytes and expression of PD-L1. Here, we present an ongoing clinical trial combining the checkpoint inhibitor pembrolizumab, the PARP inhibitor olaparib, and temozolomide for treatment of recurrent gliomas with HRD. Methods: This is an open-label, non-randomized phase II trial of combination pembrolizumab, olaparib, and temozolomide for patients with recurrent glioma. The main study cohort (A) will consist of 52 patients with recurrent enhancing grade 2 or 3 IDH-mutant gliomas. An exploratory cohort (B) will consist of 5 patients with recurrent IDH-wildtype gliomas and mutations associated HRD. Study intervention is administered in 21-day cycles and includes pembrolizumab (200mg IV q3 weeks day 1), olaparib (200mg bid orally days 8-14) and temozolomide (50mg/m2 orally days 8-14). The primary outcome is overall response rate (ORR) in cohort A. Secondary objectives include safety and toxicity of triplet therapy, overall and progression-free survival, and best radiographic response. Exploratory objectives will describe outcomes in the IDH-wildtype cohort and associate response to tumor markers obtained through archival tissue and cell free DNA of cerebrospinal fluid. The trial includes a 6-patient safety lead-in to assess tolerability of triplet therapy. Cohort A patients must have grade 2 or 3 IDH-mutant glioma without known CDKN2A/B loss. Patients in Cohort B must have IDH-wildtype glioma with an alternate deleterious mutation involved in homologous recombination. Additional inclusion criteria include age $\geq$ 18, ECOG 0-1, and glioma recurrent after prior therapy with measurable disease by RANO. Patients must be on a stable dose of corticosteroids not to exceed 2mg/day. There are no restrictions regarding number of recurrences or prior therapies if an appropriate washout has been completed. To date, seven of 57 patients have enrolled. The safety-lead in was completed without dose-limiting toxicities. Clinical trial information: NCT05188508. Research Sponsor: MSKCC; Merck.