N2M2/NOA-20: Phase I/IIa umbrella trial of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without *MGMT* promoter hypermethylation.

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Background: Patients with glioblastoma without *MGMT* promoter hypermethylation are unlikely to benefit from temozolomide (TMZ). Trials aiming at replacing TMZ with targeted agents in not molecularly selected patient populations have failed. **Methods:** This phase I/IIa umbrella trial aimed at showing safety, feasibility, and preliminary efficacy of targeted compounds in addition to standard radiotherapy initiated within 42 days postoperatively. Molecular diagnostics and bioinformatic evaluation are performed within 28 days after surgery. Stratification for treatment takes place in five subtrials, including alectinib, idasanutlin, palbociclib, vismogedib and temsirolimus, according to the best matching molecular alteration. Patients without matching alterations are randomized between subtrials without strong biomarkers using atezolizumab and asunercept and TMZ as standard of care. Primary objective of the phase I parts of the trial was dose finding or dose validation. In the phase IIa trials, centrally determined progression-free survival at six months (PFS-6) is used as endpoint for efficacy with interim analyses for futility (H_o: p=0.231). **Results:** From May 2018 through July 2022, 301 patients were enrolled and 228 treated in 13 German NOA sites. The alectinib and vismodegib subtrials were closed since no molecularly matching patients were accrued; the idasanutlin subtrial was closed prior to the optimal dose at nine patients at discretion of the company providing the drug. The TMZ subtrial showed a PFS-6 of 18.52% (10/54 patients) (p=0.831) and a median overall survival (OS) of 12.1 months. Asunercept: PFS-6 of 15.4% (4/26) (p=0.8825) and OS of 12.8 months. Atezolizumab: PFS-6 of 21.4% (9/42) (p=0.660) and OS of 11.7 months. Palbociclib with patients demonstrating CDK4 amplification or CDKN2A/B codeletion: PFS-6 of 24.4% (10/41) (p=0.4823) and OS of 12.6 months. Temsirolimus with patients demonstrating mTOR activation: PFS-6 of 39.1% (18/46) (p=0.0109) and OS of 15.4 months. The regimen-limiting toxicity (RLT)-rate is 34.8%, which is insignificantly above the predefined unacceptable rate for RLTs of 30%. Most RLTs had severity grade 3, one RLT had severity grade 4. No RLTs resulted in death. **Conclusions:** N^2M^2 allows for elaborate molecular testing being integrated into the treatment decision and efficient determination of treatment activity for patients with newly diagnosed glioblastoma. There is clinical activity of temsirolimus in patients with tumors harboring an activated mTOR pathway although this is not positively prognostic without mTOR inhibition; there is no clinical activity for asunercept and atezolizumab in not molecularly selected patients and also palbociclib in molecularly selected patients. Clinical trial information: NCT03158389. Research Sponsor: German Cancer Aid; German Ministry of Science and Technology.

Alliance A071401: Phase II trial of abemaciclib in patients with grade 2/3 meningiomas harboring somatic NF2 or CDK pathway alterations.

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Background: Systemic treatments are limited for patients with meningiomas that have progressed after surgery and/or radiation. Loss of *NF2*and *CDKN2A/B*are common in higher grade meningiomas and promote meningioma progression in preclinical models. We evaluated the efficacy of abemaciclib, a cyclin-dependent kinase (CDK) 4/6 inhibitor, as part of Alliance umbrella trial A071401, a genomically driven phase II study in recurrent or progressive meningiomas. **Methods:** Eligible patients (pts) with grade 2/3 tumors and *NF2* mutations or CDK pathway alterations were treated with abemaciclib 200 mg orally twice daily until progressive disease. Two co-primary endpoints were used: progression-free survival at 6 months (PFS6) and response rate (RR) by Macdonald criteria; the trial would be declared positive if either endpoint was met. Twenty-four evaluable pts provided >85% power to detect a PFS6 >41.5% (vs. null 15%; alpha =0.02). The threshold for promising results for PFS6 was 8+/24 pts. For RR, 24 evaluable pts provided >89% power to detect RR >20% (vs. null 2.5%; alpha = 0.021). The threshold for promising results for RR was 3+/24 pts. **Results:** Of 83 pts screened while the abemaciclib arm was open between September 15, 2021 and October 3, 2022, 36 eligible pts received treatment. The mean number of treatment cycles administered was 7 and median follow-up since start of treatment was 11 months. The first 24 pts that met eligibility criteria and began treatment were considered evaluable for the primary endpoint analysis. Of the 24 pts evaluated, 58% were female and the median age was 62 years. The observed PFS6 rate was 54% (13/24 pts, 95% confidence interval 33-75%), thus the study met PFS6 endpoint. No objective responses were observed. Of the 36 pts who started treatment, eight had a grade 3 and two had a grade 4 adverse event at least possibly related to treatment. Grade 3 toxicities included anemia (2), neutropenia (2), leukopenia (1), blurry vision (1), diarrhea (2), fatigue (2), ALT elevation (1), dehydration (1), hyperkalemia (1), hyponatremia (1), dizziness (1), acute kidney injury (1), and thromboembolic event (1). Grade 4 toxicities included ALT elevation (1), AST elevation (1) and vomiting (1). **Conclusions:** Abemaciclib was well tolerated and resulted in an improved PFS6. The overall trial endpoint was met. Abemaciclib warrants further investigation for the treatment of patients with progressive grade 2/3 meningiomas. Support: U10CA180821, U10CA180882; UG1CA189867 (NRG Oncology); Eli Lilly; https://acknowledgments.alliancefound.org. Clinical trial information: NCT02523014. Research Sponsor: None.

Niraparib efficacy in patients with newly-diagnosed glioblastoma: Clinical readout of a phase 0/2 "trigger" trial.

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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 PK threshold is met. **Methods:** Presumed newly-diagnosed GBM patients received 4 days of niraparib (300/200 mg QD) prior to planned resection 3-5 (cohort 1) or 8-10 hours (cohort2) following the last dose. Tumor tissue (Gadolinium 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 *ex vivo* irradiation of surgical vs non-irradiated tissue. A PK 'trigger' determined eligibility for the Phase 2 component of the study and was defined as unbound [niraparib] > 5-fold biochemical IC50 (i.e., 19 nM) in non-enhancing tumor. Patients with MGMT unmethylated tumors in excess of the PK threshold were eligible for Phase 2 dosing of niraparib plus radiotherapy followed by a maintenance phase of niraparib monotherapy. **Results:** All Phase 0 patients (n=46) met the PK threshold. In non-enhancing tumor regions, the mean unbound concentration of niraparib was 335.1 nM (n=43) for cohort 1 and 331.9 nM (n=3) for cohort 2. PAR suppression after ex vivo radiation was observed in 73% of the patients (24/33). Nineteen of 27 (70.3%) patients with unmethylated tumors were enrolled into Phase 2. Five patients in Phase 2 experienced Grade 4 thrombocytopenia related to niraparib. All adverse events resolved without sequelae. At time of data cutoff, median progression-free survival was 11.7 months. Mature overall survival (OS) data will be reported for the first time. **Conclusions:** Niraparib achieves pharmacologically relevant concentrations in non-enhancing, newly-diagnosed GBM tissue in excess of any other studied PARP inhibitor. Accompanying PD effects were observed in patient tumor tissue. For the first time, we report on the clinical efficacy of the study. A global Phase 3, open-label, randomized 2-arm study comparing niraparib versus temozolomide in adult patients with newly diagnosed, MGMT unmethylated glioblastoma is being planned. Clinical trial information: NCT05076513. Research Sponsor: Ben and Catherine Ivy Foundation & Barrow Neurological Foundation.

2003 Oral Abstract Session

Efficacy and safety of the vebreltinib in patients with previously treated, secondary glioblastoma/IDH mutant glioblastoma with PTPRZ1-*METFU*sion *GEN*e (FUGEN): A randomised, multicentre, open-label, phase II/III trial.

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Background: Although gliomas with mutated IDH have an improved prognosis compared to gliomas with wild-type IDH, IDH-mutant gliomas carry a high risk of malignant transformation from low-grade gliomas into high-grade gliomas within 10 years, resulting in poor prognosis. However, effective targeted drugs for high-grade gliomas are still lacking. Here, we report data from the FUGEN study of Vebreltinib, the first completed phase II/III trial of sGBM / IDH mutant glioblastoma patients with previously treated, PTPRZ1-MET Fusion gene positive. **Methods:** In this open-label, phase II/III trial, we randomly assigned, in a 1:1 ratio, 84 patients with Histologically confirmed secondary GBM or IDH-mutant GBM to receive twice-daily oral vebreltinib in 300 mg dose or the investigator's choice of chemotherapy (temozolomide [100-150 mg/m^2/day, 7days on followed by 7 days off] or cis-platinum [80-100 mg/m^2 for 3 days] combined with etoposide [100mg/m^2/day for 3 days]) every 28 days. The primary endpoint was overall survival (OS), and the secondary endpoints were progression-free survival (PFS) and objective response rate (ORR). **Results:** 42 patients of the vebreltinib group and 39 patients of the chemotherapy group were included in the full analysis set. After a median follow-up of 4.44 months, the median OS in the vebreltinib group and chemotherapy group was 6.31 months (95% CI, 4.44-8.77) and 3.38 months (95% CI, 2.37-4.27), respectively. The HR for OS was 0.52 (90% CI, 0.32-0.85; P = 0.009). The median PFS in the vebreltinib group and chemotherapy group was 1.87 months (95% CI, 1.41-2.76) and 1.05 months (95% CI, 0.95-1.77), respectively. The HR for PFS was 0.54 (95% CI, 0.33-0.88; P = 0.014). No significant differences were observed in ORR (9.5% vs. 2.6%) for the vebreltinib group and chemotherapy group. Treatment-related adverse events of grade 3 or 4 were reported in 7% of the patients in the vebreltinib group, as compared with 12.2% of those in the chemotherapy group. No treatment-related deaths were observed. **Conclusions:** These results of the FUGEN trail support the use of vebreltinib as the first target therapy in patients with previously treated, PTPRZ1-MET fusion gene positive, secondary glioblastoma / IDH-mutant glioblastoma, and shed light on a novel therapeutic pathway in the landscape of IDH-mutant high-grade gliomas. Clinical Trials Information: NCT06105619 and ChiCTR2300077783 Research Funding:Beijing Pearl Biotechnology Co., Ltd. and Avistone Biotechnology Limited. Clinical trial information: NCT06105619. Research Sponsor: Beijing Pearl Biotechnology Co., Ltd. and Avistone Biotechnology Limited.

Survival outcomes associated with first-line PCV or temozolomide in combination with radiotherapy in IDH-mutant 1p/19q-codeleted grade 3 oligodendroglioma.

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Background: Patients with IDH-mutant 1p/19q-codeleted grade 3 oligodendroglioma ($O3^{IDHmt/Codel}$) benefit from adding alkylating chemotherapy to radiotherapy (RT). However, the optimal chemotherapy regimen between Procarbazine, CCNU, and Vincristine (PCV) and Temozolomide (TMZ) remains unclear given the lack of randomized trial data comparing both regimens. **Methods:** The objective was to assess the overall (OS) and progression-free (PFS) survival associated with first-line PCV/RT versus TMZ/RT in patients diagnosed with $O3^{IDHmt/Codel}$. We included patients with histologically-proven $O3^{IDHmt/Codel}$ (according to WHO criteria) from the French national prospective cohort study POLA. All tumours underwent central pathological review. OS and PFS from surgery were estimated using Kaplan-Meier method and Cox regression model. **Results:** 305 newly-diagnosed $O3^{IDHmt/Codel}$ patients treated with RT and chemotherapy between 2008 and 2022 were included. 67.9% of patients (n=207) were treated with PCV/RT and 32.1% with TMZ/RT (n=98). Median follow-up was 78.4 months (IQR=44.3-102.7). Median OS was not reached (95%CI: NR-NR) and 140 months (95%CI: 110-NR) in the PCV/RT and TMZ/RT groups, respectively (log-rank $P<0.0001$). On univariable analysis, there was a significant difference in favor of PCV/RT in both 5-year (PCV/RT: 89%, 95%CI: 85-94; TMZ/RT: 75%, 95%CI: 66-84) and 10-year OS (PCV/RT: 72%, 95%CI: 61-85; TMZ/RT: 60%, 95%CI: 49-73), which was confirmed in the multivariable Cox model adjusted for age, type of surgery, gender, ECOG performance status and *CDKN2A* homozygous deletion (HR 0.53 for PCV/RT, 95%CI: 0.30-0.92, P=0.025). **Conclusions:** In patients with newly-diagnosed $O3^{IDHmt/Codel}$ from the POLA cohort, first line PCV/RT was associated with better OS outcomes compared to TMZ/RT. Our data suggest that the improved safety profile associated with TMZ comes at the cost of inferior efficacy in this population. Further investigation using prospective randomized studies is warranted. Research Sponsor: None.

Evaluation of VAL-083 in GBM AGILE, a phase 3 registration platform trial for newly diagnosed and recurrent glioblastoma.

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Background: GBM AGILE (NCT03970447) is a phase 2/3 Bayesian adaptive registration platform trial testing multiple therapies efficiently against a common control (C) with a primary endpoint of overall survival (OS). VAL-083 (VAL) is a DNA targeting agent that, independent of O6-methylguanine DNA methyltransferase promoter methylation status, targets the N7 position of guanine residues and facilitates inter-strand DNA crosslinks, leading to DNA double-strand breaks and cell death. It entered the trial in January 2021, and it is the 2nd arm (of 6) to complete its evaluation. **Methods:** Patient subtypes considered in GBM AGILE are newly diagnosed methylated (NDM), ND unmethylated (NDU), & recurrent disease (RD). C is temozolomide (in ND) & lomustine (in RD). Arms open to all 3 subtypes are evaluated in 5 prospectively defined signatures (sig): NDU, NDM, RD, all ND and All. Randomization to C is 20% in each subtype. Exp arms in GBM AGILE have 1 or 2 stages. Efficacy is based on OS hazard ratio (HR) of arm/C. Efficacy goal is a final Bayesian probability $\geq$ 98% for HR $<$1.00 in combined Stages 1 & 2. Arms stop accruing in Stage 1 if they reach max sample size (N) or drop for futility or safety. Exp arms in Stage 1 are adaptively randomized with allocation being proportional to an arm's current probability of having $\geq$ 30% benefit in OS, P(HR $<$0.70). In stage 1, exp arms are evaluated monthly, and arms showing Bayesian predictive power (PP) $\geq$ 0.8, graduate into Stage 2 with fixed randomization in one sig. For all exp arms, follow up continues for 12 mos after accrual stops (clinical cutoff). Arms are declared futile at any monthly analysis when PP is $<$0.25 for all sigs. Open to all 3 subtypes, VAL entered as the 1st arm in NDM and was randomized 1:1 to C in this subtype until additional arms entered. The target max N for VAL in its Stages 1 & 2 were 150 and 50, resp. **Results:** At the interim after VAL reached max sample size in Stage 1, the PP for all signatures was $<$0.8 and $>$0.25 for at least one sig. Thus, VAL did not graduate nor drop for futility, but accrual stopped for maximum N in Stage 1 (see table). Final results will be presented at the meeting. Columns 2-5 show results at the interim after which VAL stopped for max N. Columns 6-8 show near final results. **Conclusions:** GBM AGILE is an efficient & effective model for phase 3 drug development. VAL did not increase OS compared to C in any glioblastoma subtype. GBM AGILE evaluated this agent in less time, at lower cost, & with fewer patients than typical registration trials & is currently evaluating several other arms. Clinical trial information: NCT03970447. Research Sponsor: None.

Sig	N for C	N for VAL	Mean HR	CI*	PP	Mean HR	CI*	PoP**
NDU	92	39	1.36	(0.61, 2.54)	0.086	0.86	(0.56, 1.26)	0.794
NDM	30	28	1.07	(0.39, 2.37)	0.286	1.00	(0.53, 1.71)	0.564
RD	225	87	1.69	(0.97, 2.67)	0.005	1.08	(0.78, 1.45)	0.345
ND	122	67	1.18	(0.53, 2.22)	0.148	0.91	(0.6, 1.33)	0.708
All	347	154	1.4	(0.87, 2.11)	0.014	0.99	(0.76, 1.26)	0.564

*Credibility Intervals.
**Posterior Probability that HR$<$1, target 0.980.

A pilot study of axicabtagene ciloleucel (axi-cel) for relapsed/refractory primary and secondary central nervous system lymphoma (PCNSL and SCNSL).

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Background: Prognosis of patients with relapsed/refractory (R/R) CNSL is poor with no standard of care treatment options. Anti-CD19 chimeric antigen receptor (CAR) T-cell therapy axicabtagene ciloleucel (axi-cel) has shown efficacy in R/R systemic large B-cell lymphoma (LBCL) and could be considered for R/R CNSL. **Methods:** We conducted a pilot study of axi-cel in patients with R/R CNS LBCL. No bridging therapy except corticosteroids was allowed after enrollment. Ommaya reservoir was placed before infusion. Patients underwent lymphodepletion with fludarabine and cyclophosphamide followed by axi-cel dosing of $2x10^6$ cells/kg intravenous infusion. The study enrolled 18 patients, of whom the first 6 patients were observed for treatment-limiting toxicities (TLTs). Primary endpoint was safety, measured by rate of TLTs and grade 3+ adverse events (AEs). Secondary endpoints included objective response rate (ORR), complete response (CR) rate, duration of response (DOR), progression-free survival (PFS) and overall survival (OS). Exploratory analyses include paired peripheral blood (PB) and CSF analyses for axi-cel pharmacokinetics, pharmacodynamics, flow cytometry, single-cell RNA-Seq. **Results:** We report the results of the entire cohort of 18 patients (13 PCNSL, 4 SCNSL, 1 concurrent systemic & ocular L) enrolled. Median age was 62 years (33-80), 8/18 were women. Median number of prior therapies was 3 (1-7). No TLTs were observed; 16/18 (89%) patients developed cytokine release syndrome/CRS (grade 3+, 0%); 8/18 (44%) developed immune effector cell-associated neurologic syndrome/ICANS, 5/18 (28%) grade 3+. Two patients developed Ommaya-related meningitis requiring explant with recovery. One patient had grade 3 seizures that resolved with anti-epileptic agents. The ORR was 94% (17/18); 67% CR (12/18). The median time to best response was 3 months. As of January 25, 2024, the median follow up was 24.2 months, median DOR 13.4 months and 9 patients had progressed. The median PFS was 14.3 months (95% CI: 6.3-NR) and median OS, 26.4 months (95% CI: 11.2-NR). Seven patients have died, all from disease progression. At the time of presentation, there will be a minimum follow-up of 12 months. Correlative data on all 18 patients will be presented at the meeting. Axi-cel pharmacokinetics in the first 12 CNSL patients was similar to that previously reported for DLBCL patients without CNS involvement in ZUMA-1 and ZUMA-7. Patients with CR demonstrated increased peak levels of pro-inflammatory cytokines. CSF CAR T cells exhibit Type I interferon (IFN) transcriptomic signature compared to proliferative signature in blood. **Conclusions:** Axi-cel was safe and well-tolerated in CNSL patients with encouraging efficacy and median PFS and durability of response of more than 1 year. There was no apparent additional risk of adverse neurologic events including ICANS from axi-cel. Clinical trial information: NCT04608487. Research Sponsor: Kite/Gilead.

High-dose almonertinib in treatment-naïve EGFR-mutated NSCLC with CNS metastases: Efficacy and biomarker analysis.

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Background: Central nervous system (CNS) metastases is inevitable for epidermal growth factor receptor (EGFR)mutant non-small cell lung cancer (NSCLC). The pre-specified analysis of the FLAURA and other phase III studies has unveiled encouraging results in patients with CNS metastasis. Nevertheless, the availability of limited biomarkers poses a challenge for the early prediction of clinical effects. **Methods:** We launched a prospective, open-label, single-arm clinical trial across multiple centers (ACHIEVE). Participants, all diagnosed with EGFR-mutated NSCLC with CNS metastases, received first line treatment with high dose Almonertinib through once-daily oral administration, with each dose being 165 mg. The primary endpoints focused on progression free survival (PFS). Concurrently, we gathered baseline and end-of-first-cycle plasma samples, subjecting them to a comprehensive 520 gene-based sequencing analysis. **Results:** A total of 63 patients were selected and enrolled between Jul 6,2021 and Aug 31,2022. The median follow-up time, until Nov 30,2023, was 538 days. The confirmed Overall Response Rate (ORR) was 88.9% (56/63), while 42.9% (27/63) of patients progressed, with a median PFS of 17.71 months (11.96-NE). Moreover, a notable 88.9% (56/63) of intracranial lesions achieved either a Complete Response (CR) in 21 cases (33.3%) or a Partial Response (PR) in 35 cases (55.6%). To guide and enhance clinical strategy selection, we conducted a comprehensive biomarker evaluation using cell-free DNA (cfDNA) sequencing. Of the 60 baseline plasmas that passed quality control, 81.7% (46/60) were identified as having at least one somatic mutation (ctDNA+). No significant differences were observed between ctDNA+ and ctDNA- groups in terms of ORR ($p = 0.33$), intracranial ORR ($p = 0.499$), PFS ($p = 0.363$, HR = 1.75), and intracranial PFS ($p = 0.562$, HR = 1.56). Furthermore, we developed a novel algorithm named MedSR (Median Short cfDNA fragment Ratio) based on cfDNA fragment distribution patterns to quantify ctDNA amount. Notably, higher baseline MedSR values (above the median) predicted significantly poorer PFS ($p = 0.001$, HR = 0.22) and intracranial PFS ($p = 0.067$, HR = 0.35), demonstrating superior efficacy compared to traditional cfDNA biomarkers like maxAF. On Cycle 2, those achieving ctDNA clearance in C2D1, regardless of their ctDNA status on baseline, exhibited significantly improved PFS ($p < 0.001$, HR = 4.63) and intracranial PFS ($p = 0.001$, HR = 5.71). **Conclusions:** High dose Almonertinib exhibited promising efficacy and maintained tolerable safety as a first-line therapy in EGFR-mutated NSCLC with CNS metastases. The novel MedSR score demonstrated potential value in predicting the efficacy of TKI treatment. Clinical trial information: NCT04808752. Research Sponsor: None.

Results from METIS (EF-25), an international, multicenter phase III randomized study evaluating the efficacy and safety of tumor treating fields (TTFields) therapy in NSCLC patients with brain metastases.

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Background: For non-small cell lung cancer (NSCLC) with brain metastases (BM) stereotactic radiosurgery (SRS) is the current preferred therapy. Due to frequent intracranial failures, there is a high unmet need for salvage therapies. Whole brain radiotherapy (WBRT) reduces intracranial failure but used less frequently due to cognitive consequences. Tumor Treating Fields (TTFields) are electric fields that disrupt cancer cell division and have shown improved survival and safety in patients with glioblastoma and metastatic NSCLC. Phase 3 METIS trial [NCT02831959] aimed to evaluate the efficacy and safety of TTFields therapy in NSCLC patients with BM treated with SRS, specifically in terms of lengthening time to intracranial progression without cognitive decline. **Methods:** Mutation negative (M-) NSCLC patients with 1–10 BM were randomized 1:1 to receive stereotactic radiosurgery (SRS) followed by Tumor Treating Fields (TTFields; 150 kHz) therapy with best supportive care (BSC) or SRS followed by BSC. Patients with Karnofsky Performance Status (KPS) ≥70, newly diagnosed with one inoperable or 2–10 supra-/infratentorial brain metastases suitable for SRS and receiving optimal extracranial disease therapy were included. Exclusions were prior WBRT and single operable or recurrent brain metastases. Primary endpoint was time to first intracranial progression (RANO-BM) based on cumulative risk. Patients were followed every two months until second intracranial progression. Cognition and patient quality of life (QoL) were evaluated. **Results:** Between July 2016 and September 2022, 298 patients were randomized. Baseline characteristics were balanced: median age was 63.5 (range 37-84) years, 37.6% females, majority of patients had a KPS ≥ 80, median time from initial NSCLC diagnosis was 1.8 months (range: 0.2-55.7), 77% had adenocarcinoma. Median treatment duration of TTFields was 16 weeks, with a median usage time of 67%. Primary endpoint, time to intracranial progression from SRS, was significantly prolonged with SRS followed by TTFields therapy with BSC vs. TTFields plus BSC arm (median of 21.9 vs. 11.3 months); HR=0.67 [0.48-0.93], p=0.02. TTFields-related AEs were mainly dermatological, and Grade ≤2. TTFields therapy also improved deterioration-free survival of global health status, physical functioning, and fatigue according to QoL, and did not negatively impact cognition. **Conclusions:** METIS study met its primary endpoint, demonstrating that TTFields therapy following SRS in mutation negative NSCLC patients with BM, significantly prolongs time to intracranial progression and could postpone WBRT, without QoL and cognition decline. Clinical trial information: NCT02831959. Research Sponsor: Novocure GmbH.

2009 Clinical Science Symposium

Longitudinal tumor-wide sampling of glioblastoma reveals diverse genomic drivers of the earliest clonal expansion at diagnosis and recurrence.

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Background: Despite decades of clinical trials, glioblastoma (GBM) remains a rapidly fatal disease. Much of therapy resistance in GBM is attributed to intratumoral heterogeneity in which subclones rapidly evolve and treatment-resistant cell populations emerge. Understanding heterogeneity at diagnosis and its relationship to the origins of recurrence are critical to selecting therapies that are efficacious across the entire tumor. However, few genomic studies go beyond analyzing single tumor samples per patient. **Methods:** A spatially oriented, whole tumor sampling approach was used to obtain 43 biopsies from 3 GBMs at diagnosis and recurrence. Pyclone and ClonEvol were applied to whole exome sequencing to reconstruct clonal evolution, FACETs identified copy number variations and HATCHet estimated tumor purity. Candidate driver mutations were evaluated in relation to the Catalogue of Somatic Mutations In Cancer. **Results:** A single founding clone and multiple subclones were identified for each diagnosis-recurrence pair. Tumor-wide clonal alterations representing initial clonal expansions of these GBMs included both canonical changes (Chr 7 gain, Chr 10 loss, CDKN2A deletion, EGFR amplification) and a diverse set of large-scale copy number variations (Chr 19, 20 gain), driver mutations (PTEN, KDR, CDH11, CNTNAP2), and fusions (LIMCH1::UCHL1, KANK::DOCK8). A second subset of alterations (Chr 8 gain, ATRX mutation), appeared to be tumor wide at diagnosis but were not identified at recurrence. Cancer drivers were also present subclonally, including CDKN2A deletion, MDM2 amplification, and mutations in NF1, and GRM3. Evolutionary trees consisted of 5 generations of clones in Patient 323 (P323), 3 in P454, and 4 in P534. Divergence of the recurrent tumors from their matched primary occurred in the second generation in P454 and P534 and in the third in P323. As a result, an average of 37% of potential drivers of oncogenesis and clonal expansion across the cohort appear after divergence. Furthermore, each recurrent tumor contained at least one tumor wide driver alteration that was subclonal or undetected at diagnosis. **Conclusions:** Whole-tumor sampling of three GBM patients at both diagnosis and recurrence identified a diversity of genomic drivers and deeper and more complex genetic roots of individual GBM than previously seen in single-biopsy studies. Tumor recurrences consistently arose from a single subclone that diverged early in evolution of the primary tumor and contained clonal drivers either not detected or subclonal in the primary—suggesting a role for these drivers in persistence and expansion. In the age of personalized medicine, our study highlights the clinical potential of tumor wide sampling in identifying therapeutic targets that could avoid heterogeneity-related therapeutic failures. Research Sponsor: U.S. National Institutes of Health; CA 151022-14.

2010 Clinical Science Symposium

Utility of circulating tumor DNA (ctDNA) from cerebrospinal fluid (CSF) for prognosis of patients with recurrent high grade glioma.

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Background: High-Grade Gliomas (HGGs) are the most aggressive primary brain tumors in adults and molecular characterization is crucial for diagnosis and optimal disease treatment. Due to the eloquent location of many HGGs, upfront or repeat tumor sampling may be suboptimal. Hence, there is an urgent need to develop alternative, minimally invasive means to obtain diagnostic information and determine the expected clinical behavior. Here we report that circulating tumor DNA (ctDNA) from cerebrospinal fluid (CSF) can be used to identify disease defining genomic alterations and to track clonal evolution. Additionally, we demonstrate that detection of CSF ctDNA is positively correlated with leptomeningeal disease and overall survival suggesting that CSF ctDNA should be integrated into clinical decision making in the clinic. **Methods:** Our study includes 313 samples from 253 patients with recurrent glioma treated at Memorial Sloan Kettering Cancer Center who underwent CSF collection for routine clinical care and were sequenced using the MSK-IMPACT targeted clinical sequencing assay (468 and 505 genes). Alterations were classified as oncogenic based on OncoKB. 17% of genomic alterations detected were identified using a secondary bioinformatics analysis, following an informed approach with less stringent mutation calling criteria and Gaussian Mixture Model to call copy number events. CSF ctDNA positivity was determined by the presence of at least one oncogenic disease defining alteration or any shared alteration with the tumor. **Results:** Within this cohort, we found 193 CSF ctDNA positive (62%) and 120 CSF negative (38%) samples. Of note, CSF ctDNA positivity was the highest amongst histone mutant tumors with 94% CSF ctDNA positivity compared to 56% CSF ctDNA positivity for IDH-WT tumors. We noticed 44% of alterations shared between the tumor and the CSF, additionally, we noted considerable tumor evolution particularly within the growth signaling pathways (e.g. *PDGFRA*). The majority of the shared alterations were clonal, and we noticed the emergence of new clonal events in the CSF. **Conclusions:** Our cohort demonstrated that patients with positive CSF ctDNA had a significantly shorter overall survival compared to those who were CSF ctDNA negative (4.83 months vs 11.83 months, HR 2.1, $p < 0.001$). In tandem with secondary clinical analysis, radiographic findings also correlated with CSF ctDNA positivity. Specifically, the presence of enhancing disease and contact of the tumor with the ventricular space were positively associated with detection of CSF ctDNA. Additionally, CSF ctDNA was associated with positive cytology in 21/21 cases (100%). With our improved bioinformatics pipeline, we hypothesize ctDNA from CSF may be used as a prognostic biomarker for survival, but confirmation requires further validation in a prospective study. Research Sponsor: None.

Efficacy and biomarker analysis of phase 2 (P2) and window-of-opportunity (WoO) cohorts of patients with recurrent glioblastoma (rGBM) treated with ST101, an inhibitor of the transcription factor C/EBPβ.

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Background: CCAAT/enhancer-binding protein β (C/EBPβ) is an important transcription factor in GBM cell maintenance and is associated with worse outcomes and resistance to chemotherapy through transcription of genes associated with cell cycle and DNA repair. C/EBPβ is also required for maintenance of immunosuppressive tumor-associated macrophages. ST101 is a first-in-class antagonist of C/EBPβ that promotes selective GBM cell death without impacting normal cell viability (Darvishi, 2022), and repolarization of macrophages toward an immunostimulatory program. In an all comers P1 study, ST101 was well-tolerated, showed significant tumor uptake, ~40 hr plasma half-life, and signal of efficacy (1PR +8SD). With strong rationale targeting C/EBPβ in GBM and evidence that ST101 crosses the BBB in preclinical biodistribution studies, cohorts in rGBM were explored. **Methods:** Pts with ≤2 recurrences of GBM were enrolled in a P2 cohort (n=30) and treated with 500mg QW. A WoO cohort of 6 pts with rGBM received 2-4 doses of ST101 500mg QW prior to surgery and resumed ST101 after surgery until progression (NCT04478279). Endpoints for the two cohorts included response, PFS and OS while the WoO cohort also included tissue analyses (GBM subtypes, tumor microenvironment (TME) characterization, ST101 tumor penetration, and C/EBPβ target engagement). Clinical data is available for both cohorts and tissue analysis is available for the WoO cohort. **Results:** Data is a snapshot as of February 1, 2024. ST101 was safe and well-tolerated in both cohorts with no discontinuations due to AEs. Pts in the P2 study show 30% DCR (1PR + 8SD), 20% 6-mo PFS and 37% OS at 1 year. Median duration of treatment is 3.4 mos with 2 pts stable and still on study for 10+ and 16+ mos. In the WoO study, efficacy from post-surgery MRI showed 67% DCR (2 PR + 2 SD) and ~50% 6-mo PFS. Median OS cannot be assessed at this early stage. The median duration of treatment is 6.02 mos with 2 pts still on study for 7+ and 10+ mos. Tissue compared before and after ST101 exposure shows ST101 uptake and C/EBPβ target engagement by IHC, and pathologic evidence of treatment effect, such as geographic necrosis, in 5/6 pts. Evaluation of tumor and TME characteristics in post-ST101 treatment tissue will be presented. **Conclusions:** Monotherapy ST101 in pts with rGBM has an excellent safety profile and results in comparable outcomes to current 2nd line treatments. ST101 crosses the BBB, engages its target, and potentially induces treatment-related necrosis. These encouraging clinical activity, safety, and tissue findings, as well as preclinical data showing additive activity in combination with lomustine, support advancing ST101 to a randomized, placebo-controlled study comparing ST101 + lomustine vs. lomustine + placebo in rGBM. We aim to initiate this study in Q3 2024. Clinical trial information: NCT04478279. Research Sponsor: Sapience Therapeutics; The Ben and Catherine Ivy foundation.

Pre-clinical modeling of navtemadlin pharmacokinetics (PK), pharmacodynamics (PD), and efficacy in glioblastoma, IDH-wildtype.

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Background: Navtemadlin (nvtm) is a potent, selective, orally available small molecule inhibitor of murine double minute 2 homologue (MDM2), which has completed a Ph 0 surgical window of opportunity study in glioblastoma, IDH-wildtype (GBM; *Lee SNO 2022*). To optimally interpret the clinical data, an extensive evaluation of nvtm PK, PD, and efficacy was performed in GBM patient derived xenografts (PDXs). **Methods:** Response to nvtm +/- radiotherapy (RT) was characterized *in vitro* and *in vivo* across a panel of GBM PDXs with various *TP53* and *MDM2* alterations. Efficacy, PK, and PD were evaluated in flank or orthotopic PDX models. p53 pathway activation was evaluated by qPCR, Western blot, and IHC. Nvtm brain penetration was evaluated in immunodeficient *abcb1a/b*$^{-/-}$ (P-glycoprotein; P-gp), *abcg2*$^{-/-}$ (BCRP), or double-knockout mice. Binding was assessed by rapid equilibrium dialysis, and nvtm concentrations by LC/MS-MS and MALDI-MSI. **Results:** Nvtm decreasedin vitro viability of *TP53*^{WT} GBM PDX explant cultures with IC_{50}s <100 nM, but was ineffective in *TP53*-mutant GBM. In flank PDX models, nvtm (100 mg/kg daily for 4 weeks) delayed tumor regrowth by 1.9 to 4.8-fold in *TP53* ^{WT} PDXs without *MDM2*amplification (n=9 models), and more markedly by 20.1 to 29.4-fold in *MDM2*amplified models (n=4; 2 PDXs did not recur). In a flank PDX dose-response study, nvtm delayed the growth of *MDM2*amplified GBM108 at 25 mg/kg vs. placebo (61 vs. 11 days; p=0.014; mean intra-tumoral nvtm = 590 nM). In contrast, growth of *MDM2* non-amplified GBM14 was delayed only at 100 mg/kg (37 vs. 15 days; p=0.082; mean intra-tumoral nvtm = 2990 nM). In both flank models, p53 target gene upregulation was similar between 25 and 100 mg/kg and did not correlate with regrowth. Nvtm was highly bound (fraction unbound = 0.090 in culture media and 0.014 in GBM tissue homogenate). In mice after oral dosing, distribution to CNS was limited by P-gp, with a brain to plasma ratio of 0.009 and unbound ratio of 0.005, whereas BCRP deficiency did not affect CNS distribution. With orthotopic GBM108, nvtm efficacy was evaluated in nude vs. efflux-deficient mice. In nude mice, nvtm was ineffective at doses up to 100 mg/kg; however, in efflux deficient mice, the mean intra-tumoral nvtm level at 25 mg/kg was similar to flank tumors (690 nM) and survival was significantly extended (134 vs. 62 days, p=0.0002) with additional benefit at 100 mg/kg (>300 vs. 62 days, p=0.002). **Conclusions:** Nvtm showed significant efficacy in *TP53* ^{WT} GBM flank PDX models but efficacy in orthotopic PDX was highly dependent on CNS penetration. Targeting nvtm levels based on the *in vitro*IC_{50} may significantly underestimate the *in vivo* effective concentration. *In vivo* studies showed lower intra-tumoral nvtm levels are required to significantly inhibit growth of *MDM2*amplified compared with non-amplified tumors. Research Sponsor: U.S. National Institutes of Health; U01CA227954; Mayo Clinic.

2013 Rapid Oral Abstract Session

A phase II trial of olaparib and durvalumab in patients with recurrent IDH-mutated gliomas.

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Background: Isocitrate dehydrogenase mutations (IDHmt) define astrocytomas and oligodendrogliomas. IDHmt results in accumulation of R-2-hydroxyglutarate (2HG), leading to epigenetic dysregulation and defective homologous recombination repair, providing a rationale for poly (adenosine 5'-diphophate-ribose) polymerase (PARP) inhibitors. PARP inhibition upregulates PD-L1 so the combination with immune checkpoint inhibition is potentially synergistic. **Methods:** Patients (pts) with recurrent high-grade IDHmt gliomas were enrolled in this phase II open-label study (NCT03991832). Eligibility included progressive disease with up to 2 prior lines of systemic therapies and ECOG 0–1. Pts received olaparib 300 mg twice daily continuously and durvalumab 1500 mg IV every 4 weeks. Simon's optimal two-stage design was used. The primary objective was overall response rate (ORR) and disease control rate (DCR) by RANO criteria. Secondary objectives included overall survival (OS), progression free survival (PFS) and safety.Exploratory biomarkers of response and resistance were assessed with serial blood samples using cell-free methylated DNA immunoprecipitation and high-throughput sequencing (cfMeDIP-seq) as well as multiplex-immunohistochemistry. **Results:** In the 29 pts enrolled between January 2020–February 2023, median age was 40.5 (range 23–66) and 41% were female. Initial tumor grade was 2 in 9, 3 in 8 and 4 in 12 pts, respectively. Median time to enrollment from tumour diagnosis was 5.9 years. All had prior resection and median number of prior systemic therapies was 2. One patient clinically deteriorated before starting treatment. ORR was 10%, 95% CI 2.2–27%, with responses in 3 pts. One pt with grade 4 astrocytoma had a complete response and remains on treatment after 33 months. The other 2 responders with grade 4 astrocytoma had response durations of 4.1 and 9.8 months. DCR was 28% (95% CI 12.7–47.2%) with 5 additional pts demonstrating stable disease. With a median follow-up of 33 months, mOS was 9.5 months (95% CI 4.3–19.3) and mPFS was 1.9 months (95% CI 1.8–3.0). There was no treatment-related grade 3–4 toxicities. Any grade toxicities included fatigue (48%), nausea (17%), diarrhea (10%), and cytopenias (3%). Using serial cfMeDIP-seq, cell free DNA methylomes comparing responders versus progressors using the top differentially methylated regions can predict treatment response with high accuracy (AUC 0.833). Post progression, differentially methylated genes converge on TGF-β and signal transduction pathways, suggesting possible mechanisms of resistance. Multi-modal analysis of long-term responders will additionally be presented. **Conclusions:** Combination treatment with olaparib and durvalumab for pts with IDHmt glioma is well tolerated but has limited efficacy in unselected pts. cfMeDIP-seq can reliably predict tumour progression providing a blood-based biomarker of treatment response. Clinical trial information: NCT03991832. Research Sponsor: Brain Canada.

2015 Rapid Oral Abstract Session

A phase Ib, window-of-opportunity study of neoadjuvant avelumab and hypofractionated proton beam therapy for recurrent radiation-relapsed meningioma.

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Background: Effective treatments for recurrent meningiomas following radiation therapy (RT) are limited. Inhibitors of the programmed-death-1 (PD-1) or programmed-death ligand-1 (PD-L1) pathway have shown modest activity for these tumors in single-arm phase 2 studies. This study aims to evaluate the immunological effects of combining anti-PD-L1 (avelumab) with proton beam therapy (PBT) for recurrent radiation-relapsed meningiomas. **Methods:** Recurrent grade 1-3 meningiomas that failed prior surgery and RT were treated with neoadjuvant avelumab (10 mg/kg IV biweekly for 6 doses) plus hypofractionated PBT (20 Gy over 5 fractions), followed by surgery and additional adjuvant avelumab (up to 6 doses). Blood samples were collected pre-avelumab, at week 4, and before surgery. Eligibility criteria include age $\geq$ 18 years, KPS $\geq$ 60, surgery suitability, dexamethasone dose $\leq$ 4mg daily, normal organ function; no prior anti-PD1/PDL1 therapy, and absence of autoimmunity. RNA-sequencing (RNAseq) and multiplex immunofluorescence (MxIF) were performed on pre- and post-avelumab tumor tissues; blood samples underwent multiplex flow cytometry (MxFC). **Results:** Between March 2018 to March 2023, 9 patients (22% grade 1, 56% grade 2, and 22% grade 3) were enrolled in the study. All completed neoadjuvant therapy, one forwent surgery due to dramatic radiological response, and two did not complete adjuvant avelumab (due to patient preference and infusion reaction). There was no dose-limiting toxicity or unexpected toxicity. After a median follow-up of 43.0 month and a minimum follow-up of 21.7 months, 8 patients have progressed, and 2 patients with progression have died. The median progression-free survival (PFS) was 19.1 months (95% CI: 15.2-23.0), with the median overall survival not yet reached. Three patients demonstrated notably prolonged PFS (37.7, 58.5 months, and ongoing). RNAseq showed significant increase in T-cell and macrophage gene expression in post-treatment tissues compared to pre-treatment. MxIF revealed a marked increase in T-cell and CD68+ macrophage infiltration in the long-PFS patients' post-treatment tissues, a pattern not observed in the short-PFS patients. Particularly, the long-PFS patients' post-treatment tissues displayed increased infiltration of CD68+HLADR+ macrophages, likely of M1-phenotype. In contrast, the pre- and post-treatment tissues from the short-PFS patients predominantly featured CD206+ macrophages, likely of M2-phenotype. A trend towards increased number of primed T cells in the peripheral blood was observed in the long-PFS patients at week 4. **Conclusions:** Avelumab combined with RT may induce an immunological response in some radiation-relapsed meningioma patients, leading to prolonged remission. Further investigations with larger prospective studies and predictive biomarkers are warranted. Clinical trial information: NCT03267836. Research Sponsor: Department of Radiation Oncology, Washington University School of Medicine; Pfizer and the healthcare business of Merck KGaA, Darmstadt, Germany.

2016 Rapid Oral Abstract Session

Phase 1b/2a study evaluating the combination of MN-166 (ibudilast) and temozolomide in patients with newly diagnosed and recurrent glioblastoma (GBM).

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Background: Ibudilast is a selective inhibitor of macrophage inhibitory factor (MIF) activity, which is upregulated in GBM and promotes stem cell growth. It also disrupts the interaction between MIF and CD74. When combined with temozolomide (TMZ) in preclinical studies, it attenuates the immunosuppressive properties of myeloid-derived suppressor cells and enhances tumor regression. This is a phase 1b/2a single-center, open-label, dose escalation study evaluating the safety, tolerability, and efficacy of the combination of Ibudilast and TMZ in newly diagnosed (nGBM) and recurrent (rGBM) GBM was initiated (NCT03782415). **Methods:** We included patients with nGBM who had completed concurrent chemoradiation, and patients with first GBM relapse who had a measurable enhancing disease. Patients were treated with monthly cycles of temozolomide (5 days of a 28-day cycle) and daily ibudilast, with a starting dose of 30 mg twice daily (BID), and escalated to a maximal dose of 50 mg BID. The primary objectives were to evaluate the safety and tolerability of the combination and determine the phase 2 recommended dose (R2PD) for phase 1b, and to evaluate the efficacy of the combination, determined by the 6-month progression-free survival rate (PFS-6) for phase 2a. A standard 3+3 design was used for phase 1b. For the rGBM cohort, a sample size of 30 provided 80% power to discriminate between historical 15% and 35% PFS-6 rates for rGBM patients. The trial would be considered successful if at least 8 patients were progression free at 6 months. Secondary objectives included overall survival (OS). Immunohistochemistry (IHC) studies were performed on archival tumor samples to evaluate factors of the tumor immune microenvironment. **Results:** 36 patients with nGBM and 26 patients with rGBM were included; 61% were males, with median age of 59 years. Ibudilast 50 mg BID was deemed to be the R2PD. PFS-6 was 44% (16 patients) in nGBM, and 31% (8 patients) in rGBM. The median OS was 21.0 months (17.7, 23.1) for nGBM and 8.6 months (7.8, 10.5) for rGBM. IHC evaluation on the original tumor tissue for patients with rGBM revealed a significantly higher CD3 positive cells infiltration, and elevated CD74 expression in tumors of patients who progressed at 5 months compared to those who did not. **Conclusions:** This study met its primary endpoint for rGBM, as the combination of ibudilast and TMZ was associated with a higher PFS-6 rate than historical controls. CD3 expression was a good predictor for tumor progression at 5 months in patients with rGBM. Encouraging preclinical studies suggest enhanced efficacy of ibudilast in GBM when combined to immune checkpoint blockade agents. Clinical trial information: NCT03782415. Research Sponsor: None.

A phase (Ph) 0/Ia study of brigimadlin concentration in brain tissue and a non-randomized, open-label, dose escalation study of brigimadlin in combination with radiotherapy (RT) in patients (pts) with newly diagnosed glioblastoma (GBM).

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Background: MDM2 inhibits tumor suppressor p53. Brigimadlin, a potent MDM2–p53 antagonist, restores wild-type (wt) p53 function and has shown early efficacy in pts with solid tumors (LoRusso et al *Cancer Disc* 2023). GBM is an area of unmet need with 5-year survival <10%. In p53 wt GBM pt-derived xenograft models, brigimadlin promotes tumor cell apoptosis and extends survival in combination with RT. **Methods:** NCT05376800 is a Ph 0/Ia open-label, single-arm trial that aims to measure brigimadlin concentration in brain tumor tissue in pts with histologically or radiologically newly diagnosed GBM eligible for resection (Ph 0) and determine the maximum tolerated dose of brigimadlin plus RT in pts with *TP53*wt, *IDH* wt, *MGMT* promoter unmethylated GBM (Ph Ia). In Ph 0, pts received one brigimadlin dose (30 mg or 45 mg) ~12–24 h before resection. Ph 0 primary endpoints are the measured total concentration and the calculated unbound concentration of brigimadlin in brain tissue homogenate from non-contrast enhancing (NCE) and contrast enhancing (CE) regions. The predefined threshold for trial continuation is 0.5 nmol/L (corresponding to IC_{50} in GBM cell lines) unbound brigimadlin in CE samples in ≥50% of pts. Brigimadlin concentration was measured using LC/MS and corrected for amount of brigimadlin in residual blood. Unbound concentration was calculated using an *in vitro* estimate of unbound fraction (f_u): 0.654% (rat brain slice). f_u in human plasma was 0.22%. $K_{p,uu}$ (ratio of unbound concentration in brain vs plasma) was calculated. Biomarker testing was performed. **Results:** Data are available for 11 pts (brigimadlin 30 mg: n=6; 45 mg: n=5). In the 30 mg group, median total brigimadlin concentration in NCE samples was 267 nmol/L (4 samples, range 86–316 nmol/L) and 332 nmol/L (6 samples, range 272–952 nmol/L) in CE samples. In the 45 mg group, median total brigimadlin concentration in NCE samples was 197 nmol/L (5 samples, range 140–347 nmol/L) and 603 nmol/L (5 samples, range 441–905 nmol/L) in CE samples. Unbound concentration exceeded the 0.5 nmol/L threshold in most cases (Table). Post-brigimadlin, an increase in selected p53 target gene expression was observed in CE vs NCE tissue. **Conclusions:** Unbound brigimadlin concentrations in CE regions in all pts receiving the low dose of 30 mg brigimadlin exceeded the 0.5 nmol/L threshold. $K_{p,uu}$ in most patients was close to 1 in CE regions. Biomarker data support target engagement in brain tissue. Our findings support continued investigation of brigimadlin in GBM. Recruitment is ongoing. Updated data will be presented. Clinical trial information: NCT05376800. Research Sponsor: Boehringer Ingelheim.

Dose, mg	Pt	Unbound Conc, nmol/L		$K_{p,uu}$	
		NCE	CE	NCE	CE
30	1.1	0.32	0.96	0.11	0.32
	1.2	-	3.06	-	0.78
	1.4	1.83	1.93	0.60	0.63
	3.2	-	5.79	-	1.47
	3.3	1.84	1.81	0.60	0.59
45	1.5	0.42	2.65	0.15	0.92
	1.7	0.01	1.34	0.00	0.26
	1.9	1.64	5.41	0.41	1.36

-, not available

2018 Rapid Oral Abstract Session

Tucatinib-trastuzumab-capecitabine for treatment of leptomeningeal metastasis in HER2+ breast cancer: TBCRC049 phase 2 study results.

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Background: Treatment options for patients with leptomeningeal metastasis (LM) are limited and prognosis is poor. Tucatinib is a potent, highly selective HER2-targeted tyrosine kinase inhibitor. The combination of tucatinib-trastuzumab-capecitabine is approved for patients with metastatic HER2+ breast cancer, with or without brain metastases, who have received ≥ 1 prior HER2-based regimens in the metastatic setting. Patients with LM were excluded from HER2CLIMB (NCT02614794). The aim of this study was to determine the benefit of this regimen in patients with HER2+ breast cancer and LM. We previously reported preliminary efficacy data, with a median OS of 10 months and a median time to CNS progression of 6.9 months. Here, we present additional data on LM objective response, provider-rated neurologic clinical exam, and patient-reported outcomes (PRO). **Methods:** TBCRC049 (NCT03501979) is an investigator-initiated phase 2 study evaluating a tucatinib-trastuzumab-capecitabine regimen in adults with HER2+ breast cancer and newly diagnosed LM. Eligible patients had a Karnofsky performance status > 50 and untreated LM (defined as positive CSF cytology and/or radiographic evidence of LM plus clinical signs/symptoms). In 21-day cycles, patients received PO tucatinib, PO capecitabine, and IV trastuzumab. The primary endpoint was OS. LM objective response was assessed using a composite of neuroaxis imaging, neurologic clinical exam, and CSF cytology, derived from RANO-LM. The clinical exam incorporated the NANO scoring tool and symptom evaluation using MDASI-BT. Up to 4 provider-rated baseline target neuro deficits were monitored. An imaging scorecard was used. PROs were assessed using the LASA and MDASI-BT tools. **Results:** Enrollment was planned for 30 patients but closed at 17 patients following FDA approval of tucatinib (April 2020). All patients (median age 53 years) had MRI evidence of LM, 15 (88%) were symptomatic, and 8 (47%) had abnormal CSF cytology. At data cutoff (7/20/21), 5 (38%) of 13 response-eligible patients achieved LM objective response per the composite criteria at first response assessment, and all 13 (100%) achieved clinical benefit (SD, PR, or CR). Notably, 7 (58%) of 12 evaluable patients with target neurologic deficits at baseline experienced improvement of deficits. All 17 completed $\geq 75\%$ of LASA and MDASI-BT PRO questionnaires at pre-specified timepoints. The mean improvement in LASA score was 13.5, indicating improved QOL and the mean improvement in MDASI-BT score was 32, indicating improved symptom burden. **Conclusions:** This is the first prospective evidence of clinically meaningful benefit including objective responses, symptom improvement, and quality of life, along with extended survival, with a systemic regimen for LM from HER2+ BC. These data support the trend toward using systemic therapy as an initial approach in CNS metastases. Clinical trial information: NCT03501979. Research Sponsor: Translational Breast Cancer Research Consortium (TBCRC); Seattle Genetics.

2019 Rapid Oral Abstract Session

Tyrosine kinase inhibitors with and without upfront CNS radiation for brain metastases in oncogene-driven non-small cell lung cancer (TURBO-NSCLC).

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Background: Newer generation tyrosine kinase inhibitors (TKI) for NSCLC with *EGFR* mutations and *ALK* rearrangements have demonstrated encouraging central nervous system (CNS) activity with CNS objective response rates, greatly improved from 1st generation TKIs. In response to these data, guideline statements have acknowledged a strategy of CNS-penetrant TKI +/- upfront stereotactic radiosurgery (SRS) for the treatment of select patients with BM. However, optimal use of upfront SRS for BM in these patients is controversial since upfront CNS radiation has been the historical standard of care, and there are limited data guiding patient management with upfront TKI alone. Additionally, results from a large multi-institutional series reported inferior overall survival (OS) with the omission of SRS in patients with *EGFR*-mutated NSCLC treated with first-generation TKI. **Methods:** Data on TKI-naïve patients with *EGFR*- and *ALK*-driven NSCLC with BM treated with CNS-penetrant TKIs +/- upfront SRS were retrospectively collected from 7 centers in the United States. Time to CNS progression (PD), local CNS PD, and OS were analyzed, with multivariable adjustment (MVA) in Fine and Gray and Cox proportional hazards models for baseline factors including age, sex, performance status, mutation, extracranial metastases, prior therapy, neurologic symptoms, and number and size of BM. **Results:** We identified 317 patients (200 TKI only and 117 TKI+SRS). 250 (79%) and 61 (19%) patients received osimertinib and alectinib, respectively. Patients who received TKI+SRS were more likely to have BM ≥1 cm ($p<0.001$) and neurologic symptoms ($p<0.001$) at baseline. The median follow-up from treatment of BM was 23 months and 26 months in the TKI and TKI+SRS groups, respectively. Median OS was similar between the TKI and TKI+SRS groups (median 41 months [95% CI: 35-NR] vs 40 months [95% CI: 40-NR], respectively; $p=0.5$). On MVA, TKI+SRS was associated with a significant improvement in time to CNS PD (HR 0.63; 95% CI: 0.42-0.96; $p=0.033$). Local CNS control was significantly improved with TKI+SRS (HR 0.30, 95% CI: 0.16-0.55; $p<0.001$), whereas no significant differences were observed in distant CNS control. Subgroup analyses demonstrated greater CNS control benefits with TKI+SRS in patients with BM ≥1 cm. **Conclusions:** This is the largest multi-institutional study comparing strategies of CNS-penetrant TKIs +/- upfront SRS in TKI-naïve patients with oncogene-driven NSCLC. The addition of SRS improved time to CNS PD and local CNS control but not OS. Patients with BM ≥1 cm may benefit the most from upfront integration of SRS. Research Sponsor: NIH/NCI Cancer Center; P30 CA008748.

Multivariable analysis competing risk regression models for CNS PD, Local PD, and OS.

	N	HR	95% CI	p-value
CNS PD				
TKI	200	—	—	
TKI+SRS	115	0.63	0.42, 0.96	0.033
Local PD				
TKI	200	—	—	
TKI+SRS	115	0.30	0.16, 0.55	<0.001
OS				
TKI	200	—	—	
TKI+SRS	115	0.96	0.64, 1.44	0.8

2020 Rapid Oral Abstract Session

Stereotactic radiosurgery in patients with small cell lung cancer and 1-10 brain metastases: A multi-institutional, phase II, prospective clinical trial.

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Background: Stereotactic radiosurgery (SRS) as opposed to whole brain radiation (WBRT) represents the standard of care for patients with a limited number of brain metastases. Brain metastases from small cell lung cancer (SCLC), however, represent an exception to this dogma, given that prior trials evaluating SRS in lieu of WBRT excluded patients with SCLC due to the historical role of prophylactic cranial irradiation (PCI) and concerns relating to neurologic decline and death when WBRT is omitted from upfront management. We conducted a prospective, multi-center, phase II trial of SRS in patients with SCLC and 1-10 brain metastases to determine how rates of neurologic death compared to historical controls managed with WBRT. **Methods:** Following approval from the Dana-Farber/Harvard Cancer Center IRB, we opened a single-arm, multi-center, phase II trial to investigate SRS in patients with SCLC and 1-10 brain metastases naïve to prior brain-directed radiation including PCI (NCT03391362). Prior resection of a brain metastasis was permitted. Patients with leptomeningeal disease were excluded. Metastases <2cm in maximal size were generally managed with SRS to 20 Gy; larger tumors, or those near sensitive structures, were dose reduced to 16-19 Gy or managed with fractioned SRS (SRT) to 30 Gy in 5 fractions. Gross totally resected brain metastases received SRT to 25 Gy in 5 fractions. We sought to determine, as the primary endpoint, whether or not use of SRS in lieu of WBRT would lead to meaningfully higher rates of neurologic death (HR 1.61, corresponding to a 1-year event rate of 26.7% relative to a historical 1-year rate of 17.5% in patients previously managed with WBRT at our center), with 90% power and a one-sided alpha error of 5%. Neurologic death was defined as marked, progressive, radiographic brain progression accompanied by corresponding neurologic symptomatology without systemic disease progression / systemic symptoms of a life-threatening nature and was assessed by a panel of 2-3 neuro-radiation oncologists. **Results:** Between 3/2018 – 4/2023, 100 patients were enrolled across 4 centers. The median age was 68 years (IQR 63 – 74 years). The median number of brain metastases was 2 (IQR 1 – 3); 16 (16%) of patients underwent prior neurosurgical resection. On study, 66 (66%) patients were treated with SRS alone while 32 (32%) were treated with SRT to at least 1 site; 2 patients died of systemic disease progression before study treatment. The median overall survival was 10.3 months. In total, 19 neurologic deaths were observed, relative to 62 systemic deaths. The neurologic death rate at 1 year was 11.0% (95% CI 4.8% – 17.2%). **Conclusions:** Our prospective, multi-institutional study demonstrated modest rates of neurologic death when SRS as opposed to WBRT is used in patients with SCLC and 1-10 brain metastases and represents the largest prospective experience to date. Clinical trial information: NCT03391362. Research Sponsor: Joint Center for Radiation Therapy.

2021 Rapid Oral Abstract Session

Re-irradiation in recurrent glioblastoma: PET- or MRI-based? Results of a prospective randomized clinical trial.

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Background: Re-irradiation is an important treatment option for recurrent glioblastoma (rGBM). Here, we aimed to compare the oncological outcome of a re-irradiation target volume delineation based on O-(2-[18F]fluoroethyl)-L-tyrosine (FET) positron emission tomography (PET) with the one of a treatment based on contrast enhanced T1-weighted magnetic resonance imaging (T1Gd-MRI). **Methods:** GLIAA was a prospective, multicenter, randomized trial (NOA 10/ARO 2013-1, DKTK-a.). Patients with rGBM recurrence of 1-6 cm following initial radiotherapy were recruited at 14 centers in Germany and randomized 1:1 between a FET-PET- (arm A) and a T1Gd-MRI-based target volume delineation (arm B). The treatment consisted in a high-precision stereotactic re-irradiation with 39 Gy in 13 fractions. The primary endpoint was progression-free survival (PFS) from randomization. Secondary endpoints included overall survival (OS), local tumor control, and toxicity. **Results:** From November 26, 2013, to September 2, 2021, 271 patients were assessed for eligibility and 200 were randomized. 98 patients in the FET-PET arm and 97 patients in the T1Gd-MRI arm were treated per protocol. Median PFS was 4.0 months (95% confidence interval [CI] 3.7-5.2) in the FET-PET arm and 4.9 months (95% CI 3.7-6.0) in the GdT1-MRI arm (one-sided stratified log-rank test p=0.98; adjusted HR for the experimental versus the control arm 1.14 [95% CI 0.85-1.52], p=0.39). Median OS was 9.4 months (95% CI 7.8-11.1) in arm A and 9.0 months (95% CI 7.6-10.5) in arm B (HR 1.01 [95% CI 0.75-1.37], p=0.92). Local control rate at 12 months was 22% in the FET-PET arm (95% CI 14%-31%) and 20% in the GdT1-MRI arm (95% CI 12%-29%). Radiation necrosis as adverse event was documented in 25.5% of cases in arm A and in 21.6% in arm B. Of the 239 patients who received the FET tracer, 3 reported 5 severe adverse events in the timespan of 7 days after PET. No event was related to the application of the tracer. **Conclusions:** In this trial, FET-PET-based re-irradiation of rGBM was not superior to the GdT1-MRI-based treatment. Consequently, both options remain valid in this setting. Stereotactic re-irradiation with 39 Gy in 3 Gy fractions was shown to be safe and the FET-PET investigation was well tolerated in all cases. Due to the inclusion of FET-PET-positive patients only, our results do not impact the known diagnostic role of FET-PET in differentiating rGBM progression from post-therapeutic changes. Clinical trial information: NCT01252459. Research Sponsor: Deutsche Krebshilfe.

2022 Poster Session

Dual-agent immunotherapy for prevention of melanoma brain metastases: A real-world analysis of 8686 patients.

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Background: Melanoma brain metastases (MBM) are a common endpoint among patients with advanced melanoma and prognosis is poor. Strategies for MBM prevention can prolong life and reduce morbidity. Dual agent immunotherapy (dIT) has been paradigm-changing in management malignant melanoma management. Recent clinical trials have supported the role of dIT for upfront management of small, asymptomatic MBM. Yet, its potential role in extending brain metastasis-free survival (BMFS) and decreasing MBM incidence overall has not been explored. The objective was to compare MBM incidence, median overall survival (OS), and BMFS in melanoma patients treated with dIT versus single immunotherapy (sIT). **Methods:** A real-world deidentified database collating clinical information from 92 organizations (TriNetX, Inc.) was queried. Melanoma patients without brain metastases prior to immunotherapy were stratified by treatment (anti-CTLA4 [sIT] and combination anti-CTLA4/ anti-PD1 [dIT]) and propensity-score matched. MBM incidence was measured within 5 years post-IT initiation. A complementary single-institution retrospective cohort study analyzed melanoma patients treated from 2012-2019. Median OS and BMFS were compared via log-rank tests and multivariate Cox proportional-hazards models. A competing risk analysis was performed to measure the cumulative incidences of MBM and death without MBM. **Results:** TriNetX identified 8,686 melanoma patients who received immunotherapy (4,585 dIT; 4,101 sIT). MBM incidence was 13.4%, and 19.3%, for the dIT and sIT cohorts, respectively ($p < 0.0001$). DIT was associated with a lower likelihood of developing MBM compared to sIT (RR [95%CI], 0.69 [0.62-0.77]). After propensity-score matching on demographics and comorbidities, MBM incidence was similarly 13.3% and 18.5% for the dIT and sIT cohorts, respectively. On single-institution analysis, 130 melanoma patients were included (87 dIT; 43 sIT with anti-CTLA4). In patients with stage IV disease, median OS was 1.70 and 3.66 years for the sIT and dIT cohorts, respectively (p=0.6). Median BMFS was 1.56 and 2.36 years in the sIT and dIT cohorts respectively (p=0.76). On multivariable Cox proportional hazard regression analysis, NRAS mutation was significantly correlated with a worse prognosis for BMFS. **Conclusions:** These data highlight the impact of combination anti-CTL4/ anti-PD1 immunotherapy in decreasing MBM incidence. The potential primary prophylactic role of dIT in MBM warrants prospective exploration, including mechanistic understanding. Research Sponsor: None.

2023 Poster Session

Clinical and molecular features and survival in thyroid cancer with brain metastases.

Carly C. Barron, Thais Baccili Cury Megid, Yangqing Deng, Erick Figueiredo Saldanha, Gordon Taylor Moffat, Richard Thomas O'Dwyer, Aruz Mesci, Jelena Lukovic, Richard Tsang, Ozgur Mete, Monika K. Krzyzanowska, Lucy Xiaolu Ma; University of Toronto, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Princess Margaret Cancer Centre, Toronto, ON, Canada; Princess Margaret Cancer Centre, Toronto, Canada; Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Princess Margaret Cancer Center, Toronto, ON, Canada; University Health Network, Toronto, ON, Canada

Background: Brain metastases (BM) in advanced thyroid cancer are rare; however, they may be underreported as staging brain imaging is not routine. Prognostic features and molecular alterations for this group are poorly described. We characterized the clinical and molecular features of thyroid cancer with BM and evaluated differences in survival. **Methods:** In this single-center retrospective analysis, patients with metastatic radioactive iodine refractory well-differentiated, poorly-differentiated, or medullary thyroid carcinoma seen at the Princess Margaret Cancer Center from 2007-2022 were included. Electronic medical records were reviewed to collect clinicopathologic and treatment data. All patients had tumor next-generation sequencing (NGS) by a targeted gene panel. Overall survival (OS) from initial medical oncology consultation was analyzed using the Kaplan-Meier method and univariate and multivariate Cox proportional hazards models. **Results:** Of 248 patients with advanced thyroid cancer, 41(17%) were diagnosed with BM. The median interval from thyroid cancer diagnosis to BM development was 6.49 years (y) (IQR 3.51- 14.35 y). The median age at the time of BM diagnosis was 63.6 y and 23 (56%) were male. Most (76%) were asymptomatic at the diagnosis of BM and 80% had an ECOG of 0-1. Among patients with well-differentiated histology, 27 (18%) developed BM, while 7 (12%) with poorly-differentiated and 7 (19%) with medullary thyroid cancer developed BM. The most common molecular alterations included BRAFV600E (n=19), TERT (n=11), RAS (n=9), RET (n=8), and FANCA (n=3). Patients were treated with surgery (n=5), stereotactic radiation (n=21), whole brain radiation therapy (n=12), or a combination of both (n=2). OS was similar in patients with BM compared to those without (6.05 vs 6.45 y). There were no differences in histology or molecular alterations between patients that developed BM compared to those who did not. The median survival from the time of BM was 3.23 y. Patients with BM with $\geq$4 lesions had worse survival (0.52 vs 5.09 y, p=0.01). There were no differences in survival based on histology, symptoms, treatment or molecular alterations among those with BM. **Conclusions:** This is one of the largest reported thyroid BM cohorts and the first with complete NGS. The prevalence of BM in our cohort was higher than previously described, often diagnosed incidentally. Screening for BM in advanced thyroid cancer may detect higher rates, offering prognostic insights. While the number of BM was predictive of survival, molecular alterations did not predict BM development or survival and larger studies are needed. Research Sponsor: None.

2025 Poster Session

Effect of breast cancer receptor subtypes and CSF cytology status on survival for patients with leptomeningeal disease.

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Background: Leptomeningeal disease (LMD) in metastatic breast cancer (MBC) carries a poor prognosis. Data on the effect of BC sub types and CSF cytology results on overall survival (OS) are lacking. This single institution retrospective study compares OS among MBC with LMD across BC sub types and CSF cytology results. **Methods:** This study included patients (pts) diagnosed with MBC LMD from Jan 2010 to Jan 2023. BC sub types were defined as (1) ER positive (+)/HER2 negative (-), HER2+, triple-negative BC (TNBC), (2) HER2 0 [immunohistochemistry (IHC) score 0], HER 2 low [IHC 2+ with fluorescence in-situ hybridization negative OR IHC 1+], HER2+. ER and HER2 positivity were defined per ASCO/CAP criteria. CSF cytology sub types were CSF+ (for malignant cells), CSF-, and CSF not tested. Baseline characteristics were compared using Fisher's Exact and Wilcoxon rank-sum tests. OS among sub types was evaluated using Kaplan-Meier analysis and compared using log rank test. For multivariate analysis, a step wise model selection was performed after inclusion of sub type of interest; and variables meeting entry ($p<0.10$) and staying criteria ($p<0.05$) were included in final Cox model. **Results:** Out of 219 patients screened, 69 pts were registered. Median OS and associated 95% confidence interval (CI) within BC sub types in analyses 1 and 2 and CSF sub type analysis are shown in the table. OS in analysis 1 was not significantly different by BC sub types. In multivariate analysis, TNBC sub type had significantly shorter OS than ER+/HER2- group [Hazard Ratio (HR) 2.64, 95% CI (1.23, 5.80) (p=0.04)] after adjusting for interval from MBC to LMD diagnosis and CSF cytology status. OS by BC sub types in analysis 2 was not significantly different in unadjusted and multivariate analyses. CSF- group had significantly better OS compared to CSF+ or CSF not tested group in unadjusted analysis (Table) and multivariate analysis [CSF+ vs CSF- HR 4.5 95% CI (1.75-12.11); CSF not tested vs CSF- HR 2.91 95% CI (1.45-6.26), overall p=0.002]. **Conclusions:** This single institution study on MBC pts with LMD showed that BC receptor sub types were significantly associated with OS when adjusted for the interval from MBC to LMD diagnosis and CSF cytology group. This study showed significantly improved OS among patients with negative CSF cytology compared to those with positive cytology or those not tested, indicating a novel prognostic value of CSF cytology (currently on diagnostic value) for MBC LMD. These findings will be further validated. Research Sponsor: None.

Analysis	Sub Type Comparison	Median OS, Months (95% CI)	Log Rank p-value
Analysis 1	ER+/HER2- (n=33)	8.0 (3.0, 24.8)	0.17
	HER2+ (n=12)	5.7 (1.6, not estimated (NE))	
	TNBC (n=24)	3.2 (1.1, 5.0)	
Analysis 2	HER2 0 (n=21)	3.6 (1.1, 12.7)	0.23
	HER2 low (n=32)	6.9 (2.3, 18.1)	
	HER2+ (n=12)	5.7 (1.6, NE)	
CSF cytology	CSF+ (n=16)	3.5 (1.6, 12.7)	0.04
	CSF- (n=18)	13.4 (4.9, 61.9)	
	CSF not tested (n=35)	3.3 (1.4, 6.9)	

Radiosurgery to 5 or more newly diagnosed brain metastases in the systemic therapy era.

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Background: Stereotactic radiosurgery (SRS) is an ablative modality for focal treatment of brain metastases (BM) and is standard of care for limited BM. Suitability for SRS has historically been linked to number of BM, with up to 4 BM considered amenable to SRS. JLGK0901 revealed no difference in overall survival (OS) and similar rates of adverse events for patients with 5-10 vs. 2-4 BM. Evidence supporting for SRS for >10 BM is limited. As systemic treatments have evolved to include agents with improved central nervous system (CNS) efficacy and OS, the role of SRS warrants re-evaluation. **Methods:** We retrospectively reviewed patients from a single institution with ≥5 BM treated with SRS with no prior history of brain radiation 2015-2022 on an IRB-approved protocol. Clinical history, including sex, histology, Karnofsky performance status (KPS), extracranial disease status and systemic regimen used before and after diagnosis of BM, was reviewed. Systemic regimens were categorized based on potential for CNS efficacy as 1) none: no evidence, 2) weak: single agent immunotherapy or known but limited data on CNS efficacy, or 3) strong: multiple agents with known CNS efficacy, single agents with strong CNS efficacy. Kaplan-Meier method was used to estimate survival with log-rank test used to evaluate differences in survival curves. Cox proportional hazards modeling was used to evaluate differences in CNS progression-free survival (CNS-PFS) and OS. **Results:** 558 patients (48% female) who received SRS to ≥5 BM (range 5-23) were identified. Primary histologies included: 36% non-small cell lung cancer; 22% melanoma; 14% breast; 7% renal; 5% gastrointestinal; 15% other. Median OS was 11.0 months and did not differ between patients with 5-9 (n=441) vs ≥10 BM (n=117) (median OS 11.1 vs. 10.0 months; p=0.53). Median CNS-PFS was 6.6 months and did not differ between 5-9 vs ≥ 10 BM (median CNS-PFS 6.4 vs. 7.7 p=0.86). On univariate analysis, high KPS (HR 0.96; p<0.001) was associated with improved OS. Histology (p=0.14), BM number (p=0.53); average BM volume (p=0.48), and systemic disease status (p=0.17) were not associated with OS. Change of systemic therapy at time of SRS was associated with improved OS (HR 0.58; p<0.001) and CNS-PFS (HR 0.63; p<0.001). Amongst patients with systemic therapy change, regimens with increased CNS efficacy compared to prior therapy were associated with improved OS (HR 0.59; p<0.001) and CNS-PFS (HR 0.65; p=0.002). **Conclusions:** In this large, retrospective analysis of patients with ≥ 5 previously untreated BM treated with SRS, we found no association between BM number and CNS-PFS or OS. Change in systemic therapy, particularly to agents with CNS efficacy, was associated with improved outcomes. While limited by biases inherent to retrospective analyses, these results suggest patients with larger number of BM (≥10) are appropriate for SRS, especially when changing to systemic therapy with CNS penetrance. Research Sponsor: None.

Tumor reactive T cells from the cerebrospinal fluid of patients with leptomeningeal disease from melanoma.

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Background: Leptomeningeal disease (LMD) is a devastating complication from cancer, with a median survival of 6-8 weeks. The incidence of LMD is highest in melanoma (5-25%) carrying the worst prognosis. Adoptive cell therapy (ACT) using tumor-infiltrating lymphocytes (TILs) showed complete and durable responses in patients with advanced metastatic melanoma. CSF-derived T cell populations in LMD shift to more exhausted phenotypes compared to extracranial and brain metastases. *Ex vivo* large T cell expansion can overcome this shortfall, with adoptive T cell transfer representing a novel therapeutic approach to treat melanoma LMD (M-LMD). The goal of this study is to optimize rapid CSF-derived tumor reactive T cell expansion in M-LMD, and evaluate the immune microenvironment in CSF compared to peripheral immunity and anti-tumoral response. **Methods:** CSF was collected from M-LMD patients (n=6) via lumbar puncture or Ommaya. Cells were plated following established TIL culture protocols to determine optimal expansion conditions i.e.: 1) 6000 IU/mL IL-2, 2) IL-2+OKT3, 3) IL-2+anti-4-1BB agonistic antibody, 4) IL-2+IL-7+IL-15+IL-21, 5) IL-2+anti-CD3/CD28 human dynabeads, & 6) IL-2+anti-CD3/CD28/CD137 human dynabeads. After 4 weeks, T cells were propagated via rapid expansion protocol (REP) and phenotyped for CD4+ and CD8+ T cells with flow cytometry. T cells were co-cultured for 18-24 hours with HLA-matched melanoma cell lines to assess functionality, and IFN-y levels evaluated in supernatant. Ongoing studies are evaluating other biomarkers i.e., chemokines via Luminex. To examine the expanded TCR clonotypes, TCR beta seq was done in CSF-derived T cells at different times point of expansion and peripheral T cells. **Results:** Collected CSF yielded an average 8.12e4 viable cells for expansion (range 5e2-2.43e6). After initial culture in IL-2, 61.9% of samples showed increased cell yield with an average 101.68-fold expansion (range 2.35-1054). PreREP T cells were predominantly CD4+ (45.7%). REP was completed with a 100% success rate (mean 187.47-fold expansion). Post-REP flow cytometry analysis revealed similar results with further expansion of T cells. Additional culture supplements (Methods #2-6) produced similar expansion with a reduced T cell input requirement and demonstrated the potential to enrich for CD8+ T cells. M-LMD T cells were highly functional, producing substantial levels of IFN-y in response to HLA-matched melanoma cell lines. Anti-CD3/CD28 produced a larger expansion of T cells with higher levels of IFN-y. Preliminary TCR beta sequencing data revealed a distinct clonal distribution between peripheral and CSF-derived T cells. **Conclusions:** Therapies for LMD patients are desperately needed. Results demonstrate successful expansion of T cells *ex vivo* from CSF in M-LMD. Results raise potential to use autologous CSF-derived T cells as therapeutic strategy for patients with LMD. Research Sponsor: None.

Genomic biomarkers of CNS-specific outcomes in patients with breast cancer brain metastases.

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Background: The diagnosis of brain metastasis (BM) is a life- and prognosis-altering event for patients with breast cancer (BC). The standard of care for the management of limited BM remains ablation with stereotactic radiosurgery (SRS). There are no established genomic biomarkers to guide CNS-directed treatment among patients with breast cancer brain metastases (BCBM). **Methods:** We retrospectively reviewed clinical and genomic features of a cohort of patients who received SRS for newly diagnosed BCBM between 2010 and 2021 at Memorial Sloan Kettering Cancer Center (MSK). Next-generation genomic sequencing (NGS) was performed using the MSK-IMPACT assay, covering all exonic and selected intronic regions for up to 505 genes. Time-to-CNS progression (TTCP) and overall survival (OS) were analyzed using multivariable Fine-Gray and Cox proportional hazards models, respectively, adjusted for clinically relevant factors. Relevant clinical factors and genomic alterations present at an instance at 5% or greater were included in the univariate and multivariate analyses, completed for the overall cohort and BC receptor subtypes. **Results:** From 2010-2021, 260 patients were identified; 123 (47%), 74 (28%), and 63 (24%) patients had hormone receptor-positive (HR+), HER2+, and triple-negative (TN) disease, respectively. 116 (45%) patients had 1 BM and 184 (71%) patients had at least 1 BM greater than 1 cm in axial diameter. Median follow up for the overall cohort was 18 months (Interquartile range (IQR) 9, 36). Among patients who progressed, median TTCP was 6 (IQR 4, 13) and 6 (4, 13), 11 (5, 18), and 4(3, 8) months for the overall cohort, and HR+, HER2+, and TN subgroups, respectively. Median OS was 19 (95% CI 16, 23) and 15 (13, 21), 58 (39, –), and 13 (11, 20), for the overall cohort, and HR+, HER2+, and TN subgroups, respectively. In the overall cohort, shorter TTCP was associated with TN subtype, >5 BMs, and pathogenic alterations in MYC, AGO2, PTEN, AURKA, and NF1 ($p < 0.05$); decreased OS was associated with non-HER2+ subtype, presence of extracranial metastatic disease, and oncogenic alterations in TP53, CDH1 and NF1 ($p < 0.05$). In stratified analyses by receptor subtype, shorter TTCP was associated with oncogenic alterations in GAB2 and PTEN in the HR+ subgroup, AURKA, DDR2, and NF1 in the HER2+ subgroup, and with MYC and RB1 in the TN subgroup ($p < 0.05$). **Conclusions:** In this large clinico-genomic analysis of CNS-specific outcomes in BC, we identified clinical and putative genomic biomarkers associated with BCBM receiving SRS that could be used to risk stratify patients and optimize treatment strategies. Research Sponsor: None.

Real-world use of a CSF circulating tumor cell assay in the diagnosis and management of leptomeningeal metastasis.

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Background: The diagnosis of leptomeningeal metastasis (LM) can be challenging due to variability in clinical symptoms, radiographic, and cerebrospinal fluid (CSF) findings. The National Comprehensive Cancer Network (NCCN) guidelines recommend assessment of circulating tumor DNA (ctDNA) to increase sensitivity of tumor cell detection and assess the response to treatment. We hypothesize that the real-world use of an assay for the direct detection and enumeration of circulating tumor cells (CTCs) in the CSF is clinically useful for accurate diagnosis of LM, particularly in an early stage of disease. **Methods:** We report a series of 55 patients treated at our institution with a cancer diagnosis and either neurological symptoms or radiographic findings that suggested LM. All patients underwent a lumbar puncture, assessment for CSF CTCs, and conventional hospital-based cytology testing between 6/1/2020 and 8/1/2023. Survival data cutoff was 12/31/2023. Patient outcomes are reported. **Results:** 55 patients were tested, and 30 patients were found to be positive for CTCs and diagnosed with LM. Only 10 patients were concurrently positive for CTCs and cytology at our institution, whereas 20 patients with positive CTCs had a negative or ambiguous cytology. No patients with a negative CTC result (25 patients) were subsequently diagnosed with LM, whereas 4 patients with a positive CTC result remained without progressive neurological symptoms. 5 patients diagnosed with LM were alive at the time of data cutoff. The histologic breakdown for LM was: breast (11), non-small cell lung cancer (NSCLC) (16), gastrointestinal (GI) (3). Median overall survival (OS) was longer in patients with a positive CTC and negative cytology result compared to patients with concurrent positive CTC and cytology (172 vs. 63 days, $p = 0.06$). Median OS was also longer in breast cancer LM compared to NSCLC LM (235 vs. 63 days, $p = 0.008$). Most patients diagnosed with LM received therapies including Ommaya reservoir placement, intrathecal chemotherapy, and/or radiation. **Conclusions:** The use of a CSF circulating tumor cell assay aided the diagnosis of LM and led to timely initiation of treatment. A negative result of the CTC assay was associated with ruling out LM. Diagnosis of LM with the CTC assay and negative cytology was associated with longer survival, possibly due to earlier treatment initiation, and not solely a lead time bias. Breast cancer LM patients had improved survival compared to NSCLC and GI cancer patients, possibly due to more effective treatment options. Research Sponsor: None.

Efficacy of intrathecal delivery of peptide-pulsed type 1 conventional dendritic cell vaccine for the treatment of breast cancer-associated leptomeningeal disease in preclinical models.

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Background: Approximately 5% of advanced stage breast cancer (BC) will develop leptomeningeal disease, a rare form of metastasis in the meninges, a membrane surrounding the brain and spinal cord. The prognosis for BC-LMD is dismal and currently available treatments are ineffective. For example, intrathecal (IT) therapy such as trastuzumab, and proton cranial spinal radiotherapy have only showed modest success. Dendritic cells are a master regulator of the immune system and play a critical role in bridging the innate and adaptive immune response. Here, we used a novel preclinical model to administer MHC class II peptide-pulsed conventional Type 1 dendritic cells (cDC1s) intrathecally in mice that harbor either HER2+ or triple negative breast cancer (TBNC) LMD. Our murine BC-LMD murine data lead us to open a Phase 1 clinical trial of cDC1s in HER2+ and TNBC LMD (NCT05809752; in progress). **Methods:** Our lab developed a "murine Ommaya" which mimics the clinically used Ommaya reservoir and allows for repeated intrathecal (IT) injections of novel drugs at 3 – 7μl volume directly into the CSF. We next developed a pipeline for screening immunogenic MHC class II peptides from tumor-associated oncodrivers and using these targets to generate tumor-targeting cDC1s. We tested the resulting vaccines in a preclinical model that IT delivers peptide-pulsed cDC1 cell therapy directly into the BC-LMD microenvironment. **Results:** We tested the efficacy of treatment in HER2+ LMD and TNBC-LMD models and found effective responses; LMD mice that received IT cDC1 therapy exhibited reduced tumor burden and prolonged survival that was significantly better than systemic therapy. Approximately 70% of mice from HER2+ LMD and 30% from TNBC LMD demonstrated complete responses. This was CD4+ T cell dependent. Notably, cured mice also showed signs of resistance against LMD recurrence upon rechallenge. Subsequent single cell RNA-seq (scRNA-seq) analyses of the CSF showed a shift in the innate immune landscape found in untreated LMD to an adaptive immune landscape. In addition, we noted the elevated secretion of Th1 proinflammatory cytokines such as IFN-γ in the CSF. This was recapitulated in the CSF samples of patients enrolled in an ongoing phase 1 trial, where early data showed IT cDC1 triggered a high concentration of several proinflammatory cytokines. **Conclusions:** Our preclinical data suggest IT cDC1 vaccine is effective against BC-LMD and prevents LMD recurrence. We are currently investigating the mechanism(s) by which IT cDC1-initiates the CD4 Th1 adaptive immune response against LMD. By employing an scRNA-seq approach, we hope to further determine the roles of different immune cells and their subtypes in the CSF to IT cDC1s in mice and in patients. A future approach includes testing IT cDC1 platform in LMD from other cancers (e.g. melanoma etc.).
Research Sponsor: U.S. Department of Defense CDMRP BCRP.

Novel non-invasive method for measuring intracranial pressure for drug delivery and other neurologic disorders.

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Background: Leptomeningeal carcinomatosis (LC) represents an area of largely unmet clinical need, and intrathecal (IT) drug delivery is often used as treatment (tx). In addition, LC can lead to hydrocephalus, sometimes also during IT treatment . Intracranial pressure (ICP) changes might occur during IT administration, and could have serious clinical consequences, including neurological damage and tracking ICP changes might be beneficial. EnClear Therapies has developed a novel way of externally monitoring ICP through attachment via a minimally invasive intrathecal catheter. In addition, the device allows for easy sampling of CSF, and could aid in tracking of biomarkers longitudinally. Here, we describe this new sensor device and provide data on its use in non-human primates. **Methods:** The EnClear device utilizes a pressure sensor that easily attaches via a Luer lock to any IT catheter, such as an Ommaya placed intraventriclular and/or lumbar intrathecal. The associated software continually displays the pressure waveform data from the sensor on a monitor with the subject's pressure, respiration and heart rate. To test the sensitivity of the system, ICP response to a bolus drug infusion of 2 ml was measured before, during, and after infusion, in 7 non-human primates as change in pressure (ΔP) following volume (ΔV) administration, known as intracranial elastance or compliance ($\Delta P/\Delta V$). **Results:** When ICP was measured at both intraventricular and lumbar IT locations, there were good concordance between the two sites in each subject (0.88 correlation coefficient). Transient elevation of ICP during drug delivery in non-human primates was evident, climbing to as high as 20-40 mmHg. Of note, the ICP was variable between subjects with identical infusion volume. Intracranial elastance was calculated for each subject during infusions and resulted in a range of 12 to 36 mmHg; a 3-fold difference in elastance was measured between subjects. **Conclusions:** In 7 healthy non-human primates, the EnClear ICP measurement device has demonstrated that changes to cranial volume and pressure response can be measured with external sensors with reliable correlation between the two measurement locations. While pressure was consistent between locations, intersubject variability was seen despite identical drug and volume administration. Use of the pressure waveforms from EnClear's device can be used to enable clinicians to understand individual patient brain elastance and leverage this knowledge for personalized drug delivery. Intersubject variability further supports the need for ICP monitoring and this platform provides a less invasive manner to do this. An upcoming clinical study in patients with LC is planned to compare EnClear's new device directly to the standard of care, the implanted Camino ICP monitor. The applications go beyond LC, and will benefit patient care for other CNS disorders. Research Sponsor: EnClear Therapies.

Identification of pharmaceutics with selective activity against melanoma-associated leptomeningeal disease using patient-derived circulating tumor cells.

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Background: Patients with advanced stage of melanoma may develop leptomeningeal disease (LMD), a rare form metastasis in the meninges. Unfortunately, there are currently no rationally designed treatments for melanoma-associated LMD (M-LMD) and the prognosis is dismal; with survival measured in weeks. A major barrier to developing effective therapies for this disease is the absence of model systems, such as patient-derived cerebral spinal fluid-circulating tumor cell (PD-CSF-CTC) models to identify and assess novel therapeutics. Added to this challenge is the difficulty of collecting and analyzing M-LMD specimens in the clinic and at autopsy. To address these hurdles, we have made considerable progress recently in overcoming these barriers via CSF and tissue collection (in clinic and rapid autopsy) and successfully propagating CSF-CTCs from M-LMD patients *in vitro* and in xenograft mouse models. These valuable resources have allowed us to perform proteomic and transcriptomic analyses of CSF and PD-CSF-CTCs, respectively. By comparing M-LMD -*omics* data against those from normal brain and extracranial disease, we have found unique LMD-specific biological pathways. In this study, we identified clinical compounds that could target these biological pathways and have efficacy against PD-CSF-CTCs *in vitro* and *in vivo*. **Methods:** PD-CSF-CTCs were propagated from individual M-LMD patients. Next, we have developed a 384-well high throughput cell-based assay and performed a pilot screening of more than 1,400 FDA-approved small molecule compound library using Echo to identify pharmaceutics that inhibit cell proliferation. Clinical compounds with the highest sensitivity were selected for validation of efficacy *in vivo* via intrathecal (IT) delivery of patient-derived cell lines to establish M-LMD xenografts. **Results:** Of the 1,436 FDA-approved small molecule compounds, 57 (~3.9%) exerted 95% proliferation inhibition and 20 (~1.4%) had 100% killing effect in PD-CSF-CTCs and murine melanoma cell lines. The compounds with the highest sensitivity include ponatinib (EC50: 1.85 – $4.06e^{-06}$), sorafenib (EC50: 9.57 – $9.77e^{-06}$), ceritinib (EC50: 1.84 – $2.05e^{-06}$) and homoharringtonine (HHT) (3.63 – $4.11e^{-08}$). In a randomized murine M-LMD preclinical trial, we selected HHT, since it is a cephalotaxine ester compound that can penetrate the brain. Our results show that HHT was well-tolerated *in vivo*given systemically or IT via a murine Ommaya. We found M-LMD mice that received 14.5ng HHT (g.d. IT) showed significant prolonged median survival (control vs. HHT, *P* value: 0.0006; Mantel Cox test). **Conclusions:** This is the first demonstration of an approach that allows for the rational development of therapeutics in M-LMD. Results will provide crucial new insights into biology and will identify drug candidates that may be suitable for future clinical trials. Research Sponsor: Chemical Biology & Molecular Medicine Program.

Evaluation of survival outcomes in patients with solid organ cancer with brain metastasis treated with exacta encylopedic tumor analysis based treatments.

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Background: Brain metastasis in solid organ cancers presents a challenging scenario with an adverse prognosis and limited systemic treatment options. Treatment of such patients becomes more challenging because most drugs can't cross the blood-brain barrier, besides the treatment being too harsh for sensitive brain parenchyma. Moreover, these patients are frequently excluded from clinical trials, reflecting concerns about their poor prognosis influencing trial outcomes and potentially distorting efficacy data. While almost all cancers metastasize to the brain, cancers of the breast, lungs, kidney and melanoma carry a higher risk. **Methods:** The Resilient Study, a Phase-II, single-arm, open-label interventional trial, focused on evaluating the efficacy of Exacta Encyclopedic Tumor Analysis (ETA)-guided treatment for a range of solid organ cancers in patients who had failed multiple lines of treatment and were broadly refractory. 143 patients were recruited out of whom 126 patients were evaluable. Prior to treatment initiation, all patients underwent PET-CT and MRI scans to assess the extent of the disease. 9 out of 126 patients (7.1%) were found to have metastatic deposits of the brain comprising 6/21 patients (29%) of breast cancer, 2/5 patients (40%) of lung cancer, and 1/15 patient (7%) of colorectal cancer. Utilizing freshly biopsied tumor tissue (primary/lymph node/liver) and peripheral blood, Exacta ETA was performed, encompassing gene mutations, gene expression, and in vitro chemosensitivity profiling of viable tumor cells. Exacta ETA-derived personalized therapy recommendations were administered to patients. Follow-up data for OS was collated. **Results:** Median overall survival (OS) was not reached at the time of analysis. By considering the OS values censored at the interim (most recent follow-up), the median OS was 9.7 months (95% CI 7.06 - 12.3 months; range: 1 month – not reached) among patients without brain metastases (n = 117, 92.8%) and 10 months (95% CI 2.6 - 15.9 months; range: 2.6 months – not reached) among patients with brain metastases. **Conclusions:** Our data shows that personalized Exacta ETA-guided treatments resulted in almost similar OS for patients with brain metastases as seen in patients or without brain metastases. These findings stand out as significant considering the poor outcomes with Standard of Care treatments in patients with brain metastases. Clinical trial information: CTRI/2018/02/011808. Research Sponsor: None.

PD-L1, tumor mutational burden (TMB) and long-term survival in patients with non-small cell lung cancer (NSCLC) and brain metastases.

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Background: Brain metastases (BM) affect up to 50% of patients with NSCLC and are associated with poor prognosis in patients with non-targetable genomic alterations. Radiation forms the typical mainstay of intracranial management in such patients given the historically guarded intracranial efficacy of most systemic options. Immunotherapy-based approaches have shown promise but the extent that patients with BM may display extended survival with combination radiation- and immunotherapy-based approaches remains unclear. **Methods:** We identified 160 patients harboring non-squamous NSCLC with 486 newly-diagnosed BM between 2015-2023 managed with brain-directed radiation (either stereotactic-based, SRT or whole brain radiation therapy, WBRT) and immune checkpoint inhibition within 3 months of radiation at Dana-Farber Cancer Institute/Brigham and Women's Hospital (Boston, MA). PD-L1 tumor expression was categorized as <1%, 1-49%, 50-89%, and ≥90% based on immunohistochemistry. TMB was assessed via targeted next-generation sequencing. Cox-proportional hazards regression was used to assess all-cause mortality while Fine-Gray competing risks regression was used to assess other time-to-event based outcomes. **Results:** The median number of BM was 3 (IQR 1-7). Neurosurgical resection in advance of radiation was performed in 51/160 (32%) pts. SRT was used in 130/160 (81%) versus 30/160 (19%) patients treated with WBRT, respectively. Median follow-up time was 30.1 months (mo). Higher PD-L1 expression was associated with significantly longer overall survival (OS) with a median survival in patients with PD-L1<1%, 1-49%, 50-89% and ≥90% being 11.8, 14.4, 29.5 and 33.1 months, respectively (Table). Similarly, time to systemic death (TTSD) was longer in patients with higher PD-L1 expression, while time to neurologic death (TTND) was not different across categories. Higher TMB (≥10 vs. <10 mutations/megabase) was not associated with significantly longer OS, TTSD or TTND. **Conclusions:** Higher PD-L1 tumor expression was associated improved all-cause mortality, largely driven by reduction in systemic death. A significant percentage of patients with a very high PD-L1 displayed long-term survival, highlighting the potential importance of multimodality therapy in such patients, and demonstrating that clinicians should be cognizant of treatment-associated long-term toxicities in this population. Research Sponsor: None.

Outcomes	OS		TTSD		TTND	
PD-L1 groups	Median (mo)	p	Median (mo)	p	Median (mo)	p
<1%	11.8 [8.0-17.2]	Ref.	22.7 [16.8-NR]	Ref.	7.2 [5.2-9.6]	Ref.
1-49%	14.4 [12.6-35.3]	0.17	29.3 [19.6-NR]	0.44	7.3 [5.8-9.5]	0.087
50-89%	29.5 [17.0-NR]	0.043	NR [17.5-NR]	0.039	11.0 [6.0-20.7]	0.67
≥90%	33.1 [17.8-NR]	0.026	61.7 [40.6-NR]	0.040	10.8 [8.5-28.3]	0.10
TMB						
<10	17.5 [15.0-22.3]	Ref.	19.2 [16.6-49.6]	Ref.	7.7 [6.0-9.0]	Ref.
≥10	23.0 [17.7-36.0]	0.56	40.9 [36.0-NR]	0.17	9.7 [6.1-15.4]	0.74

Development of clinically accessible nomograms to predict risk of brain metastases at baseline and follow-up in patients with non-small cell lung cancer.

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Background: Brain metastases (BM) are a common complication in non-small cell lung cancer (NSCLC). Reliable models predicting risk of BM development are lacking, hindering effective CNS screening and patient prognostication. In the era of precision medicine, these are important gaps in our knowledge. The aims of this study were to1)evaluate published BM risk-stratification algorithms, and 2) develop nomograms to predict BM incidence. **Methods:** Using a retrospective cohort of NSCLC patients from Penn State Health (2011-2020), we *1*) evaluated the performance of published BM risk-stratification algorithms systematically identified, and 2) developed nomograms to predict risk of BM incidence. For *Aim 1*, published algorithms were benchmarked using AUROCs calculated from logistic regression models. For *Aim* 2, cox-proportional hazard models were trained using L1-regularization, and nomograms were constructed to predict BM risk at 6-month, 1-year, and 2-year follow up. Two separate nomograms were developed: Model T0 used only clinical and imaging data available at time of diagnosis, while Model T1 leveraged additional molecular characteristics and treatment history. All models were trained using 70% of data and tested using 30% of data. Time-dependent AUROC metrics for nomograms were calculated using a cumulative sensitivity and dynamic specificity-based estimator. **Results:** Our cohort included 1904 patients (median age 68, range: 38 to 94 years, BM incidence 22.8%). *Aim 1*: 12 published algorithms were identified that used variables consistently available in patient charts. Among these, the Zhang 2021 model was the best predictor of cumulative BM risk (AUROC [95% CI] = 0.89 [0.85-0.93]). *Aim* 2: Model T0 was trained using age at diagnosis and clinical TNM stage and predicted BM incidence at 6-month, 1-year and 2-year follow up with AUROCs of 0.87, 0.85, and 0.87, respectively. Model T1 was trained with additional predictors, including number of extra-cranial metastatic sites, treatment history (e.g., radiation, surgery, chemotherapy, etc.), and mutation profile (EGFR, KRAS, ALK, BRAF), and achieved AUROCs of 0.90, 0.89, and 0.91 at 6-month, 1-year and 2-year follow up, respectively. Distant metastases at time of NSCLC diagnosis (HR [95% CI] = 3.38 [2.28, 4.99]) and number of extra-cranial metastatic sites (HR [95% CI] = 1.75 [1.54, 1.99] per each additional metastasis) were the strongest independent predictors of BM risk. **Conclusions:** Based on one of the largest NSCLC cohorts to date, we have developed clinically accessible nomograms for prediction of BM development. This tool can be readily applied toward prognostic modeling and risk stratification, refinement of practice guidelines for CNS screening, and patient counseling. Research Sponsor: None.

Tumor treating fields (TTFields) therapy in patients with glioblastoma: Long-term survival results from TTFields in Germany in routine clinical care (TIGER) study.

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Background: Tumor Treating Fields (TTFields) therapy has demonstrated significant improvements in overall survival (OS) and progression-free survival (PFS) when applied with adjuvant temozolomide (TMZ) compared to TMZ alone in newly diagnosed glioblastoma (ndGBM). TTFields therapy delivers electric fields, through scalp-placed arrays, that disrupt cellular processes critical for cancer cell viability, is CE marked for WHO grade 4 glioma, and is a recommended treatment regimen for ndGBM. TTFields therapy was administered to >25,000 patients, showing no systemic toxicities and mild to moderate skin reactions being the main therapy-related adverse event. Here, we report survival and safety data from the TIGER study, the largest prospective study investigating real-world use of TTFields therapy during routine clinical care in patients with ndGBM in Germany. **Methods:** TIGER (NCT03258021), a prospective, non-interventional, multicenter, medical device study, screened patients ≥18 years of age with histologically confirmed ndGMB from August 2017 to November 2019 in 81 participating centers in Germany who had clinical indication for TTFields therapy and were within the first 3 cycles of maintenance chemotherapy treatment. The analysis presented here focuses on patients that accepted TTFields therapy. Endpoints included OS, PFS, safety, and quality of life. **Results:** In this study, 710 assessed patients agreed to participate, with 583 (82%) opting for TTFields therapy, and 429 actually commencing the treatment. This patient population represents typical GBM patients, with a median age of 58 (range 19–82) and 64.1% being male. After a total follow-up of 56.2 months, the median OS and PFS were 19.6 months (95% CI, 17.9–22.4) and 10.2 months (95% CI, 9.4–11.4), respectively. The corresponding 1, 2, 3, and 4-year OS rates stood at 79.2%, 42.4%, 31.5%, and 27.7%, while the PFS rates were 42.0%, 23.2%, 19.9%, and 17.6%, respectively. Serious AEs were observed in 68% of patients, with only 0.5% being attributed to TTFields therapy. **Conclusions:** TIGER is the largest prospective study to date on routine clinical practice in ndGBM. It reaffirms TTFields therapy's positive safety profile, and its OS and PFS survival benefits are consistent with prior reports. It also reveals promising long-term survival rates. Clinical trial information: NCT03258021. Research Sponsor: Novocure, Inc.

A phase I trial on the intra- and post-operative intracranial administration of ipilimumab and nivolumab in patients with recurrent high-grade glioma.

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Background: Intracerebral (iCer) administration (admin) of ipilimumab (IPI) and nivolumab (NIVO) plus IV NIVO following resection of recurrent high-grade glioma (rHGG) was well tolerated and showed encouraging overall survival (OS) (J. Duerinck et al. JITC 2021). The safety of additional postoperative (postop) bi-weekly intracavitary (iCav) admin of NIVO or NIVO + IPI (: first in human intracranial CTLA-4 blockade) was investigated in a phase I trial (3+3 design with cohort expansion). **Methods:** Within 24h prior to surgery, 10 mg NIVO IV was admin, followed by a maximal safe resection and injection of the brain tissue lining the resection cavity with 5 mg IPI + 10 mg NIVO, and positioning of a catheter in the resection cavity connected to an Ommaya reservoir. Only in patients (pts) receiving postop iCav IPI, 10 mg NIVO and 5 mg IPI were admin via the Ommaya at the end of surgery. Postop 1, 5, or 10 mg NIVO was admin iCav as a single agent. In subsequent pts, postop 10 mg iCav NIVO was combined with 1, 5 or 10 mg iCav IPI. All postop iCav admin were combined with NIVO 10 mg IV, and repeated Q2w (< 24w). On-treatment CSF samples were used for cytology, chemical analysis, and measurements of NIVO/IPI concentrations. **Results:** 43 pts (32 male) initiated treatment, all receiving the predefined pre- and intraop doses of IV and iCer IPI/NIVO. No unexpected AE related to the intraop treatment occurred. Postop treatment was initiated in 39 pts, all receiving 10 mg NIVO IV Q2w. Postop NIVO IV was combined with iCav NIVO 1, 5 or 10 mg in 3, 4, and 9 pts. The median number of postop IV/iCav NIVO admin was 7 (3-7), 4.5 (0-11), and 2 (1-11), resp. Next, postop iCav NIVO 10 mg was combined with iCav IPI 1, 5 or 10 mg in 10, 6, and 11 pts. The median number of postop IV/iCav NIVO + IPI admin was 3 (0-12), 4 (1-11), and 4 (0-12), resp. Dose limiting toxicity consisted of transient grade 3 aseptic neutrophilic pleocytosis with pyrexia and neurological deterioration in 1 and 3 pts treated with 5 and 10 mg IPI iCav, resp. Most frequent TRAEs were fatigue (n=24), headache (n=19), fever (n=17), and bacterial Ommaya colonization (n=11). No grade 5 AE occurred. At database lock, all pts were off study treatment, 1 pt stayed progression-free, and 5 were alive (mFU 80w (31-140)). OS compared favorably against a Belgian historical control cohort (469 pts; log rank p: 0.010) with an improved 1 and 2y OS rate (33 vs. 18.6% and 11.7 vs. 5.7%, resp.). Adding iCav IPI postop did not significantly alter PFS or OS. There was an elevated protein level and lymphocytic pleocytosis in >90% of CSF samples and no evidence for NIVO accumulation in the CSF (IPI under evaluation). **Conclusions:** In this first in human phase I trial on intracranial CTLA-4/PD-1 blockade in pts with rHGG amenable for resection, intraop iCer and postop iCav admin of NIVO+/- IPI was found to be feasible and safe up to a bi-weekly postop iCav dose of 1 mg IPI + 10 mg NIVO; with encouraging OS results. Clinical trial information: NCT03233152. Research Sponsor: Universitair Ziekenhuis Brussel.

Pharmacological targeting of lipid metabolism by a first-in-class SREBP-targeted degrader to treat glioblastoma.

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Background: Glioblastoma (GBM) is an incurable cancer. Patients are subjected to inevitable death by recurrence after the standard treatment, temozolomide (TMZ) and irradiation. Having the tumor-initiating ability, GBM cancer stem cells (GSCs) resist standard therapy and give rise to recurrent tumors; however, no GSC-targeted treatment has proven its efficacy in clinical trials. Therefore, we sought to discover the vulnerability of GSCs and develop a novel targeted therapy to combine with TMZ, which will enable the complete treatment of GBM without the risk of relapse. **Methods:** We assessed the datasets of GBM patients and patient-derived GSCs to discover the signaling pathways enriched in GSCs that are specifically sensitive to dysregulation. We conducted transcriptomic, metabolomic and cellular assays to verify the essentiality of the pathway in GSCs and to find the target suitable for disturbing the pathway pharmacologically. Through the chemical library screening and chemical optimization, we developed a novel compound that specifically degrades the target. We validated the on-target specificity and pharmacokinetic (PK) properties through biological and pharmacological studies. We verified the anti-cancer efficacy in combination with TMZ using the GBM orthotopic xenograft mouse model and evaluated the safety and toxicity by non-clinical assessments. **Results:** Unbiased analysis using the datasets of patients and GSCs revealed that ABCA3-related lipid metabolism is enriched in GSCs compared to non-GSCs. ABCA3 knockdown caused the disturbance in lipid metabolic homeostasis, leading to a decrease in the sterol-regulatory element binding protein 1 (SREBP1) activity to suppress the tumor-initiating capacity of the GSCs. We developed MFC0101, a novel small molecular compound to target the SREBP1 signaling pathway. MFC0101 specifically engages the SREBP cleavage-activating protein (SCAP), which binds to and stabilizes the SREBP1 protein, to block the protein-protein interaction between SCAP and SREBP1, inducing the degradation of SREBP1. MFC0101 displayed favorable PK profiles, such as high oral bioavailability (greater than 50% in dogs, rats, and mice) and blood-brain barrier permeability (brain-to-plasma ratio of 0.543 based on exposure in mice). MFC0101 showed no adverse events, even at the dose level required to reach maximal systemic exposure in the 28-day toxicity study in rats, and no geno- and cardiovascular toxicities. Notably, MFC0101, combined with TMZ, showed greater efficacy than TMZ alone in the GBM mouse model; 87.5% and 100% displayed complete remission of the tumor after the treatment of medium and high dose levels of MFC0101, respectively ($n \geq 8$ per group). **Conclusions:** MFC0101, the first-in-class SREBP1-targeted degrader, demonstrates its outstanding preclinical efficacy in synergy with TMZ and reasonable safety as a promising GBM treatment. Research Sponsor: Korea Drug Development Fund.

Outcomes and immune response after peptide vaccination targeting human cytomegalovirus antigen pp65 in children and young adults with recurrent high-grade glioma and medulloblastoma.

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Background: The human cytomegalovirus (CMV) antigen pp65 is ubiquitously expressed in high-grade glioma (HGG) and medulloblastoma but not in adjacent brain. The primary objective of this first-in-human phase I trial (NCT03299309) was to assess the safety and feasibility of a novel peptide vaccine targeting pp65 (PEP-CMV) in children/young adults with recurrent medulloblastoma and HGG. **Methods:** The vaccine is comprised of a synthetic long peptide of 26 amino acids and is administered as an emulsion in Montanide ISA 51. Patients receive a single 5-day course of temozolomide to induce lymphopenia, tetanus/diphtheria toxoid site preconditioning to promote dendritic cell migration, then PEP-CMV administered intradermally in the groin every two weeks for 3 doses, then monthly. **Results:** Forty-two patients were enrolled. Diagnoses include medulloblastoma (n=2), glioblastoma (n=21), anaplastic oligodendroglioma (n=3), anaplastic astrocytoma (n=11), and malignant glioma NOS (n=5). The median time from initial diagnosis to treatment was 24 months (range 4-35) and the median number of prior chemotherapy regimens was 4 (range 0-15). The mean age was 23.2 ± 9.3 years. 55% of patients were male. The median KPS was 80. Of the 38 patients who received PEP-CMV, the maximum grade adverse event (AE) possibly, probably, or definitely related to PEP-CMV was as follows: 17 (45%) had Grade 1 adverse events (AE), 16 (42%) had Grade 2 AEs, 2 (5%) had Grade 3 AEs (encephalopathy and pyramidal tract syndrome), and one (3%) had a Grade 4 AE (cerebral edema). One patient developed symptoms and had elevated inflammatory cytokines consistent with cytokine release syndrome (Grade 2). The median progression-free survival was 2.5 months (95% CI:2.2,3.2) and median overall survival was 6.4 months (95% CI: 3.4,7.9). The 12-month OS was 26.6% (95% CI:14,41.1%). Of the 22 patients with evaluable immune monitoring data, T cell reactivity on IFNγ pp65 ELISpot was increased after PEP-CMV delivery (median spot pretreatment vs. prior to vaccine #4: 1 vs 30, P=0.004, Table). Lower percentage of pretreatment regulatory T cells and higher percentage of terminally differentiated effector T cells at vaccine #4 were associated with longer subsequent survival. **Conclusions:** PEP-CMV is well-tolerated and elicits an antigen-specific immune response in heavily pretreated, multiply recurrent patients with a 12-month OS of 26.6%. A multi-institutional Phase II trial (NCT05096481) of PEP-CMV is opening imminently. Clinical trial information: NCT03299309. Research Sponsor: Pediatric Brain Tumor Foundation.

PEP-CMV pp65 ELISpot results.

Assessment	N	Mean Change from Baseline	SD	Minimum	Median	Maximum
Vaccine 4	22	78.2	166.9	-106	15	600
Vaccine 6	7	445.7	555.2	2	134	1290
Vaccine 8	5	492.4	683.1	6	102	1592
Vaccine 10	4	678	1002.5	10	272	2158
Vaccine 12	2	235	159.8	122	235	348
Vaccine 14	1	36	NA	36	36	36
Vaccine 24	1	8	NA	8	8	8
Progression	6	220.3	410.1	-86	99	1034

Retrospective study of ivosidenib for patients with recurrent IDH mutant gliomas.

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Background: IDH mutant gliomas are the most common primary malignant brain tumors in adults under the age of 50 and accounts for approximately 12% of all glioma diagnoses each year. While lower grade gliomas (LGG) encompassing WHO grades II and III are less aggressive than their higher-grade counterparts, treatment is not curative, and most patients develop tumor recurrence in which there are a paucity of effective treatment options. Mutations in IDH1/ 2 occur upwards of 80% of patients with LGG and drive specific epigenetic programs to dysregulate and impair differentiation leading to tumorigenesis. As such, pharmacologic blockage of IDH mutant enzymes is being actively investigated as potential treatment option. Ivosidenib (AG-120), a second-generation IDH inhibitor, is an FDA approved medication for treatment of IDH-mutated acute myeloid leukemia and has demonstrated safety and clinical activity in patients with progressive IDH mutant gliomas. We explored the efficacy of Ivosidenib in IDH mutant gliomas. **Methods:** We retrospectively analyzed patients with IDHm gliomas treated with ivosidenib in our institution. We included patients with an IDH1 mutation who received at least one cycle of ivosidenib. Data collected included patient demographics, tumor histology, tumor location, grade, 1p/19q co-deletion, MGMT, CDKN2A, TERT, EGFR, P53, PTEN mutational status, prior treatment history, duration of treatment, toxicities, radiographic response, PFS, and OS. Descriptive statistics were used to summarize patients' characteristics. The distribution of mPFS was estimated by the Kaplan-Meier method. **Results:** Between April 2010 and December 2023, we identified 33 patients that received ivosidenib. 7 patients received ivosidenib in combination with bevacizumab, 3 patients received ivosidenib in combination with radiation, and 1 patient received ivosidenib and nivolumab. The median age was 52 (range 31-81). 21 (63%) were male. The median lines of medical therapy and radiation/surgery prior to starting ivosidenib were 3.03(range 0-6) and 1.5(range 0-4), respectively. 27(81%) were grade 2, 5(15%) were grade 3, and 1(3%) were grade 4. 19(57%) had 1p/19q co-deletion. As of 12/31/2023, 48%(16) patients were alive. The median PFS was 7.52 months (1-26) and median OS 12.7 months (3-25). 11(33%) patients experienced partial response (PR), 20(60%) experienced stable disease (SD) and 2(6%) demonstrated progressive disease (PD) at 12-week assessment. Nine patients experienced adverse events: grade 1 fatigue (3), grade 1 diarrhea (1), grade 2 fever (1), grade 2 weakness (1), and grade 3 confusion (1). One patient experienced grade 4 lobar hemorrhage thought to be related to concurrent bevacizumab use. **Conclusions:** Treatment with Ivosidenib therapy was associated with a manageable safety profile. In a subset of patients, there was disease stabilization in heavily pre-treated recurrent IDH mutant gliomas. Research Sponsor: None.

CDKN2A deletion and radiation sensitivity in IDH-mutant astrocytomas.

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Background: IDH-mutant astrocytomas represent the most prevalent primary tumors in younger adults (<45yo). A substantial minority of these tumors exhibit the deletion of CDKN2A (Cyclin-Dependent Kinase Inhibitor Gene 2A). Homozygous deletion of this gene– which encodes the tumor suppressor protein p16 – is associated with a malignant phenotype and poorer prognosis in IDH-mutant astrocytoma. CDKN2A deletions are primarily observed in tumors that have received radiation therapy (RT), suggesting a potential mechanistic relationship between RT and deletion. This observation gives rise to two alternative hypotheses: either RT is causing DNA damage in irradiated cells, leading to the induction of subclonal CDKN2A deletion, or a subset of cells already possesses the CDKN2A deletion and is resistant to RT, resulting in the treatment selecting for the subsequent emergence of these cells. Here, we sought to ascertain the influence of CDKN2A deletion on IDH-mutant astrocytoma cellular response to RT. **Methods:** The antitumor effect of RT was evaluated *in vitro* using patient-derived IDH-mutant astrocytoma cells, MGG152. A homozygous CDKN2A deletion was engineered in this parental line, creating a paired line to permit an isogenic comparison between CDKN2A intact versus CDKN2A deleted tumor cells. A photon irradiator was used to deliver a range of clinically-relevant RT doses spanning from 0 to 20 gray (Gy). Differences in cell viability after a predetermined incubation period were examined and relevant statistical comparisons performed. **Results:** Dose-response curves in response to radiation therapy, comparing CDKN2A intact and deleted cell lines, were generated (Table). Both CDKN2A intact and deleted cell lines exhibited significant reductions in viability following radiation exposure at and above 2Gy ($p < 0.001$). CDKN2A-deleted cells displayed a small but significantly greater sensitivity than CDKN2A-intact at 1, 2, and 5Gy (Table). **Conclusions:** Our findings offer evidence indicating that p16 loss does not bestow radioresistance in IDH-mutant astrocytomas. These findings align with a hypothesis that radiotherapy (RT) might promote DNA damage, and consequently, subclonal CDKN2A deletion, in irradiated IDH-mutant tumors. Research Sponsor: NREF.

Radiation therapy response in CDKN2A intact versus deleted tumors.

	Percent Cell Viability (95% Confidence Interval)		
Radiation Dose (Gy)	**CDKN2A Intact**	**CDKN2A Deleted**	**p-value**
0	100.00 [93.35, 106.65]	100.00 [94.65, 105.35]	> 0.9999
0.5	95.84 [94.08, 97.60]	98.26 [86.26, 110.26]	0.5302
1	96.04 [93.07, 99.00]	83.31 [79.86, 86.76]	0.0016*
2	77.25 [71.74, 82.77]	63.39 [60.88, 65.90]	0.0003*
5	72.32 [69.64, 75.00]	46.14 [44.70, 47.57]	< 0.0001*
10	39.70 [37.07, 42.33]	40.68 [39.66, 41.69]	0.7992
20	25.41 [22.69, 28.13]	38.21 [37.44, 38.99]	0.0015*
IC50	9.698	1.628	

*$p < 0.05$.

INB-200: Fully enrolled phase 1 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: γδ T cells can target NKG2D ligands that are upregulated on tumor cells after alkylating chemotherapy exposure. IN8bio's DeltEx drug resistant immunotherapy (DRI) are genetically engineered γδ T cells expressing methylguanine-DNA methyltransferase (MGMT), which conveys TMZ resistance to enable concomitant therapy and continued surveillance against tumor cells. Updated results from the Phase 1 trial which fully enrolled adult newly diagnosed GBM patients with adequate organ function, KPS ≥ 70% follow. **Methods:** Cohorts (C) 1, 2 and 3 received 1, 3 or 6 doses (1×10^7 DRI cells/dose) into the resection cavity with 150 mg/m^2 of IV TMZ on Day (D) 1 of each Stupp maintenance cycle. The primary endpoint is safety and secondary endpoints include survival; immunologic correlative analyses are included. Dose limiting toxicities (DLTs) are defined as treatment related ≥ grade (G) 3 cardiopulmonary or hepatic toxicity, G4 toxicity exceeding 72 hours or neurologic deterioration that exceeds 2 weeks. **Results:** 23 patients were enrolled, with 11 dosed and 2 awaiting dosing (61% male; median age 68 (range: 21-74); 92% IDH-WT, 54% MGMT unmethylated). No DLTs, cytokine release syndrome (CRS) or neurotoxicity (ICANS) are reported. Most common adverse events were decreased WBC/platelet count, asthenia, fatigue, hydrocephalus, headache, decreased appetite, urinary tract infection, thrombosis and balance disorder. **Conclusions:** γδ T cells successfully infused with peripheral TMZ-based lymphodepletion evidenced with near or below normal range T, B, and NK subsets for up to 1 year. The majority of dosed patients who received DRI exceeded the expected median PFS of 7 months (5.8-8.2 months) with Stupp alone and had manageable toxicity with a continued encouraging trend in PFS. Long-term follow-up for durability of PFS and OS continue. Clinical trial information: NCT04165941. Research Sponsor: None.

Subject	Age/ Sex	IDH/ Methylation	Resection	Dose level	TMZ Maint. Cycles Received	Response	PFS (mos)	OS (mos)
001	69/M	IDH-WT, MGMT-unmethylated	Total	1	5	SD	8.3	15.6
003	75/F	IDH-WT, MGMT-methylated	Total	1	6	SD	11.9	17.7
004	21/F	IDH-WT, MGMT-unmethylated	Total	1	3	SD	7.4	9.6
007	75/M	IDH-WT, MGMT-unmethylated	Total	2	2	Un-evaluable	-	5.1
009	32/M	IDH-mutant, MGMT-methylated	Total	2	12	SD		30.9+
011	56/F	IDH-WT, MGMT-methylated	Total	2	6	SD	22.2	26.9+
014	73/F	IDH-WT, MGMT-unmethylated	Subtotal	2	6	SD	8.7+	8.7 without progression
015	73/M	IDH-WT, MGMT-methylated	Subtotal	3	5	SD	7.1	11.8
017	74/F	IDH-WT, MGMT-methylated	Subtotal	3	3	SD		8.7+
020	66/M	IDH-WT, MGMT-methylated	Subtotal	3	3			6.7+
021	57/M	IDH-WT, MGMT-unmethylated	Total	3	1			5.2+
022	53/M	IDH-WT, MGMT-unmethylated	Subtotal	3	Awaiting Dosing			2.4+
023	52/M	IDH-WT, MGMT-unmethylated	Subtotal	3	Awaiting Dosing			1.9+

Expand and pull: A new treatment paradigm for glioblastoma using a long-acting recombinant interleukin-7 and oncolytic viral therapy.

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Background: Patients with glioblastoma (GBM) face three major challenges. First, the tumor itself as well as chemoradiation treatment result in lymphopenia, which is associated with shorter survival. Second, the tumor microenvironment (TME) has a paucity of T cells and consequently, immunotherapies have failed in multiple phase 3 clinical trials for GBM. Third, a treatment resistant population of cancer stem cells (CSCs) contribute to inevitable tumor recurrence. In preclinical models, we have shown that a long-acting IL-7, NT-I7, significantly increases peripheral CD8 T cells and separately, oncolytic Zika virus (ZIKV) directly targets CSC and induces an anti-tumor CD8 T cell response. The aim of this study was to determine whether we can leverage the NT-I7 driven T cell expansion peripherally and combine it with ZIKV therapy to pull immune cells into the TME to successfully treat a highly immunosuppressive mouse model of GBM. **Methods:** SB28 syngeneic tumor cells were intracranially implanted in C57BL/6J mice. Mice were treated with NT-I7 subcutaneously on days 7 and 10 post tumor implantation, followed by intratumoral ZIKV on day 14. Mice were monitored for survival and bled weekly to assess the systemic T-cell response to NT-I7. Immunoprofiling of brain, draining lymph node, and peripheral blood via flow cytometry was done on days 17 and 21. **Results:** NT-I7 significantly expanded peripheral T cells compared to control (5,623 cells/μL vs 136 cells/μL, $p<0.05$). Cytotoxic CD8 T cells were particularly increased (4,776 cells/μL vs 47 cells/μL, $p<0.05$), with the expansion peak at day 7 after the first dose of NT-I7 and persisting for 21 days. When ZIKV was administered at the peak of the NT-I7-driven CD8 T cell expansion, the combination resulted in significant improvement in survival compared to NT-I7 or ZIKV monotherapy (median 47 days vs 35 days and 33 days, respectively, $p<0.05$). Combined NT-I7 and ZIKV treatment significantly increased TME CD8 T cell infiltration (369,814 cells/g vs 23,947 cells/g and 63,961 cells/g, respectively) as well as increased expression of interferon-γ, TNF-α, perforin, and granzyme B ($p<0.05$). Long-term survivors were protected against tumor rechallenge, suggesting that this treatment strategy confers immune memory against tumor antigens. The addition of immune checkpoint blockade with anti-PD1 antibody resulted in nearly 80% complete tumor clearance. **Conclusions:** Timing the oncolytic ZIKV injection with the NT-I7-induced peak expansion of peripheral CD8 T cells greatly increased tumor infiltration of cytotoxic T cells and improved survival in the immunotherapy resistant SB28 glioma model. This work suggests a new "expand and pull" approach for the treatment of highly immunosuppressive tumors such as GBM: priming the systemic immune system with NT-I7, followed by an oncolytic stimulus to draw them into the TME to engage and clear tumor cells. Research Sponsor: U.S. National Institutes of Health; R01NS117149; Siteman Cancer Center.

Targeting glioma stem cells with thyroid hormone suppression: Phase 1/2 trial of methimazole in patients with progressive grade 4 gliomas.

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Background: Gaseous hydrogen sulfide (H_2S), a by-product of cysteine metabolism, inhibits the growth of glioblastoma (GBM) cells and impairs GBM progression in mice. Likewise, H_2S generation and sulfhydration are decreased in human GBM specimens as compared to non-tumor controls. Thus, boosting H_2S production is a novel strategy for GBM treatment. Suppression of thyroid hormone (TH) signaling increases endogenous production of H_2S. We hypothesize that methimazole-induced hypothyroidism will enhance the efficacy of chemotherapy in WHO grade 4 gliomas by boosting H_2S production capacity (HPC) within the tumor. The goal of this trial is to provide proof of concept that suppression of TH signaling, via methimazole and subsequent augmentation of H_2S synthesis and signaling, is feasible in patients with WHO grade 4 gliomas (G4G). **Methods:** This modified phase 1/2 study evaluates the safety and efficacy of methimazole + chemotherapy with pharmacodynamic correlates in patients with progressive G4G. The main objective is a 10% increase in HPC and a 1.5-fold increase in peripheral blood sulfhydration signaling (SS). Patients who are planned for a clinically-indicated resection receive pre-op (5-7 days) and post-op methimazole with the addition of investigator's choice of chemotherapy 1 month after starting post op methimazole. Patients receive methimazole + chemotherapy until progression. Resected tumor will be assayed for HPC and for proteins relevant to H_2S production. Peripheral blood lead-acetate assays for HPC and SS are obtained at baseline, pre-op, intra-op, post-op, before the addition of chemotherapy, and before each cycle of methimazole + chemo. Key eligibility criteria: progressive G4G for whom a clinically-indicated resection is planned, and normal thyroid function with no history of thyroid disease. Patients may have had unlimited prior regimens including bevacizumab. **Results:** To date six patients (4 male) ages 49-59 years have enrolled. At all time points tested post-methimazole treatment relative to baseline age/sex matched no-methimazole control patients, there were significant increases in plasma H_2S production capacity (table). **Conclusions:** In this early cohort, it appears methimazole treatment in recurrent GBM patients enhances HPC on a systemic level. Next steps will be to measure sulfide signaling and sulfhydration alterations in patient tumor samples. The protocol is being modified to allow earlier addition (2 weeks) of post-op chemotherapy. Clinical trial information: NCT05607407. Research Sponsor: Cleveland Clinic.

Timepoint	Average Fold Increase in HPC	p-value
Pre-op (after 5-7 days of methimazole)	1.56	0.029
Day of surgery	2.86	0.0002
Post-op day 1	2.86	0.041
Cycle 1	3.00	0.023
Cycle 2	1.76	0.013

Out-of-pocket cost modeling of adjuvant radiation therapy duration in standard-of-care treatment of glioblastoma across Medicaid and Medicare plans.

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Background: The optimal radiation treatment (RT) length (6 weeks of 60 Gy in 30 fractions versus 3 weeks of 40 Gy in 15 fractions) for older adults with glioblastoma is debatable, with Level 1 evidence (PMID 15051755) revealing no difference in survival between RT regimens. However, there remains a paucity of evidence describing the role of insurance on out-of-pocket (OOP) costs for patients undergoing varying lengths of RT. This project aims to quantify expenses by insurance plans, enhancing transparency in treatment cost understanding. **Methods:** We utilized the National Comprehensive Cancer Network guidelines to determine the standard treatment protocol, including 30-fraction or 15-fraction RT with concurrent and post-radiation temozolomide for 12 cycles. The model assumes a Medicare- and/or Medicaid-eligible patient ≥ 65 years of age with glioblastoma. The total aggregate out-of-pocket (OOP) costs were determined from the sum of treatment costs, deductibles, and copays/coinsurance based on Medicaid, Original Medicare, Medigap Plan G, and Medicare Part D Rx plan over a two-year time horizon (not adjusted for inflation). All procedures were assumed to take place within the premises of an Ohio hospital. **Results:** Treatment charges include neurosurgery, neuro-oncology, and radiation oncology initial consultation, follow-up visits, diagnostic head CT, MRI, craniotomy with maximum safe resection, surveillance brain MRI, temozolomide, antiemetics, prophylactic TMP-SMX, weekly CBC, and tumor treating fields. RT-specific treatment charges include treatment planning, simulation and verification, RT delivery, and on-treatment visits. Original Medicare beneficiaries face an OOP cost of 20% for Medicare Part B claims with no cost cap for approved procedures after the deductible. Medications are covered under Medicare Part D with copays. This results in a total OOP treatment charge of $4,454.01 for 30 fractions and $3,913.86 for 15 fractions. Medigap Plan G beneficiaries face a total OOP charge of $2,387.22 for 30 fractions and $2,369.61 for 15 fractions. For Medicaid beneficiaries (assuming all treatments are approved by Medicaid), all expenses are covered without limit, resulting in no OOP expense for either treatment plan. **Conclusions:** Three-week versus six-week RT for GBM reduces OOP costs facing patients by 10%. By understanding the financial implications, healthcare providers, policymakers, and patients can make informed decisions about treatment options, and healthcare systems can develop strategies to mitigate the economic burden associated with GBM care. Research Sponsor: None.

Phase 1 study of anti–immunoglobulin-like transcript 3 (ILT3) monoclonal antibody (mAb) MK-0482 + pembrolizumab (pembro) in patients with recurrent inoperable glioblastoma (GBM).

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Background: For patients with GBM, treatment options are limited once the disease has recurred and become inoperable after standard first-line therapy. ILT3 is an inhibitory receptor expressed on monocytic myeloid cells, including tolerogenic dendritic cells and myeloid-derived suppressor cells (MDSCs). High expression of ILT3 on these immune cells has been associated with immune tolerance and suppression of T-cell function. Data have shown that GBMs have high ILT3 expression and high levels of MDSCs within the tumor microenvironment (TME). MK-0482 is a novel humanized IgG4 mAb targeting ILT3. Inhibition of ILT3 with MK-0482 may help relieve immunosuppression and improve T-cell function within the TME. In the expansion cohort of the first-in-human phase 1 study (MK-0482-001; NCT03918278), MK-0482 was evaluated in combination with pembro in a cohort of patients with recurrent inoperable GBM. The safety and efficacy data from this cohort are presented herein. **Methods:** Patients aged ≥18 y with their first recurrent inoperable GBM and a Karnofsky performance status (KPS) ≥80 were enrolled. Patients received MK-0482 750 mg Q3W + pembro 200 mg Q3W IV for up to a maximum of 35 cycles. The primary objective was to determine safety and tolerability of MK-0482 + pembro. Secondary objectives were to evaluate ORR, DCR (CR + PR + SD), and DOR by investigator assessment per Response Assessment in Neuro-Oncology (RANO). Exploratory objectives included evaluation of PFS per RANO and OS. **Results:** Overall, 25 patients were enrolled and received study treatment. At data cutoff (October 3, 2023), median follow-up duration was 9.3 mo (range, 5.6-14.5); treatment was ongoing in 1 patient. Median age was 56 y (range, 33-76). Most patients were male (72%), had a KPS of 80 (68%), and had *IDH1* wild-type tumors (88%). All patients had previously received systemic therapy: 24 of 25 (96%) received prior temozolomide and 3 of 25 (12%) received prior glasdegib. Overall, 22 patients (88%) had an adverse event (AE); 10 patients (40%) had treatment-related AEs, most commonly (≥10%) arthralgia (12%), fatigue (12%), and increased ALT (12%). Grade 3 treatment-related AEs occurred in 2 patients (8%; increased ALT [n = 1] and fatigue [n = 1]). No grade 4 or 5 treatment-related AEs occurred. Four patients (16%) experienced immune-mediated AEs (hypothyroidism, n = 2; hepatitis, n = 1; pancreatitis, n = 1); all were grade 1 or 2. Confirmed ORR was 12% (3/25; 95% CI, 2.5-31.2), DCR was 32% (8/25; 14.9-53.5), and median DOR was 11.1 mo (range, 9.9-16.6+). Median PFS was 1.4 mo (95% CI, 1.3-2.9) and median OS was 9.3 mo (6.3-13.7); 6-/12-mo PFS and OS rates were 24%/16% and 72%/36%, respectively. Biomarker data will be included in the presentation. **Conclusions:** MK-0482 + pembro had a manageable AE profile with modest antitumor activity in patients with recurrent inoperable GBM. Clinical trial information: NCT03918278. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

The TAC-GReD trial: The combination of talazoparib and carboplatin in DNA damage repair deficient recurrent high-grade glioma.

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Background: Recurrent high-grade glioma (rHGG) has a dismal prognosis with limited treatment options. Given that a high proportion of these gliomas harbor deficiencies in the DNA damage repair (DDRd) pathway, this genomic occurrence may confer synergistic lethality and sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitors. Therefore, we hypothesize that DDRd rHGG may be sensitive to the combination of a PARP inhibitor, talazoparib, and carboplatin. **Methods:** This is a prospective phase II, single-arm open-label biomarker stratified single-institution trial conducted in Hong Kong (NCT04740190). Tumor tissue was sent for comprehensive next-generation sequencing (C-NGS) to screen for genomic aberrations associated with the DDRd pathway. Patients with rHGG (WHO grade III-IV) and at least one pathogenic mutation in the DDR pathway were deemed eligible. Patients were initially treated with whole-brain radiotherapy (2 Gy/1 Fr) on C1D1. Starting at dose level 0, talazoparib (0.75mg on Days 1-4) and carboplatin (AUC 1.5 on Day 1), were administered weekly for a total of 18 cycles, followed by maintenance talazoparib. The primary endpoint was the 6-month progression-free survival (PFS-6). **Results:** 61 patients were screened and 33 patients with DDRd rHGG were enrolled, 23 males, 10 females, and a median age of 55 years (range: 29-70 years). 73% (n=24) had a baseline ECOG PS of 0-1. Among the recruited patients, 12% (n=4) were classified as WHO grade III, while the remaining 88% (n=29) were WHO grade IV. Dose level escalation was achieved in 27% (n=9) of the cohort. The 6-PFS was 29% (95% CI 16.2-51.9%) and the median PFS was 3.5 months (95% CI: 2.4-6.3 months). The OS at 3 and 12 months were 90.4% (95% CI 80.7-100%) and 30% (95% CI 17-53%), respectively. The most common grade 3-4 toxicities were neutropenia (21.2%, n=7), thrombocytopenia (18.2%, n=6) and anemia (9.1%, n=3). One patient developed a grade 4 thromboembolic event. Dose level reduction was implemented in 54% (n=18) of patients and treatment was terminated in 6.1% (n=2) due to toxicity. **Conclusions:** Talazoparib and carboplatin in a DDRd-enriched rHGG is feasible and tolerable. Additional analysis including correlation of biomarkers with long-term outcomes is underway. Clinical trial information: NCT04740190. Research Sponsor: Pfizer; The Hong Kong Neuro-Oncology Society.

Can targeting TSP-1 with gabapentin enhance survival in glioblastoma? A 20-year retrospective cohort study.

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Background: Molecularly-defined cellular subpopulations of glioblastoma secrete high levels of the synaptogenic protein thrombospondin-1 (TSP-1) which promotes functional integration of tumor into neural circuity. A greater extent of glioma-neuronal crosstalk portends worse survival for patients. In preclinical studies, gabapentin was shown to inhibit TSP-1, in turn disrupting neuronal synaptogenesis and neuronal activity-dependent glioblastoma proliferation; however, clinical survival data is lacking. We aim to determine whether treatment with gabapentin is associated with improved survival and reduced serum TSP-1 in a retrospective cohort of patients with IDH-wildtype glioblastoma. **Methods:** Newly-diagnosed, IDH-wildtype glioblastoma patients who received care at the UCSF Brain Tumor Center between 1997-2017 were included in this study. Kaplan-Meier curves and multivariate Cox proportional-hazards models, controlled for age, MGMT promoter methylation status, preoperative tumor volume, and extent of resection, were used for survival analyses. Differences in serum TSP-1 measured by ELISA for gabapentin treated patients and matched non-gabapentin treated controls were assessed using unpaired two-tailed student's t-test. Control samples were matched 2:1 by age, tumor volume, and extent of resection. After 2005, patients were treated with chemoradiation with concurrent and adjuvant temodar. **Results:** Among 379 adult patients with glioblastoma, 36 (9.5%) were treated with gabapentin. The median daily dose of gabapentin was 600 mg (IQR: 300-900 mg). There were no significant differences between gabapentin treated and non-gabapentin treated patients by age (0.06), sex (p=0.14), or race (p=0.52). Median overall survival for gabapentin treated and non-gabapentin treated patients was 20.8 months (IQR: 11.7 - 32.1) and 14.7 months (IQR: 8.9-23.5), respectively (p= 0.02). On Kaplan-Meier survival analysis, overall survival was longer for gabapentin treated patients compared with non-gabapentin treated patients (p=0.005). In the multivariate Cox proportional-hazards model, gabapentin use was associated with decreased hazard of death (HR 0.67, p=0.030). Mean serum TSP-1 in gabapentin-treated patients was significantly lower than in the matched control group (10181 ng/ml vs 17015 ng/ml, p=0.017). **Conclusions:** Gabapentin use is associated with a survival benefit for patients with glioblastoma, possibly mediated through a reduction in TSP-1. This promising result lays the foundation for future prospective studies to further evaluate TSP-1 as a circulating prognostic biomarker as well as to explore the therapeutic benefits of gabapentin as a life-prolonging treatment for patients with newly diagnosed glioblastoma. Research Sponsor: None.

Safety and efficacy of CyberKnife radiosurgery plus anlotinib hydrochloride in patients with recurrent glioblastoma: A prospective phase II single-arm study.

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Background: Glioblastoma (GBM) is a tumor known for its highly vascular nature and limited treatment options upon disease recurrence. While Bevacizumab which target VEGF-A has gained approval for treating recurrent glioblastoma, the multi-target tyrosine kinase inhibitor Anlotinib has the ability to directly target Vascular Endothelial Growth Factor Receptor (VEGFR), Platelet-Derived Growth Factor Receptor (PDGFR), and Fibroblast Growth Factor Receptor (FGFR). Theoretically, its anti-angiogenic effect may exceed that of Bevacizumab, and preliminary studies have shown its therapeutic efficacy in recurrent GBM (rGBM), indicating promising treatment potential. This study aims to present findings regarding the effectiveness and safety of combining Anlotinib with stereotactic radiosurgery (SRS) in treating patients with rGBM. **Methods:** Patients who underwent surgery, standard radiotherapy, and temozolomide chemotherapy and were diagnosed with recurrence based on Response Assessment in Neuro-Oncology (RANO) criteria and/or biopsy were eligible for inclusion. Each patient underwent CyberKnife SRS (25Gy/5fx) in combination with oral administration of Anlotinib (12 mg, daily, days 1–14/3 weeks) until encountering disease progression or experiencing intolerable adverse effects. The primary objective was the investigator-assessed median overall survival (OS) using the Response Assessment in Neuro-Oncology (RANO) criteria. **Results:** Between December 2019 and July 2023, 22 patients (median age: 55 years; range: 28–70) were included. According to RANO criteria, 21 patients exhibited tumor response, with 6 achieving complete response, resulting in an objective response rate of 95.5%. Additionally, one patient maintained stable disease without progression. Median progression-free survival (PFS) was 9.1 months (95% CI, 7.5–24.7), with a 6-month PFS rate of 85.7% (95% CI, 71.9–100.0). Median overall survival was 19.5 months (95% CI, 10.6–46.8). Common adverse events included hand-foot skin reactions (40.9%), hypercholesterolemia (27.3%), and hypertension (22.7%). Four patients experienced grade 3 adverse events, accounting for an 18.2% incidence rate. Therapy discontinuation due to ischemic stroke (grade 3) occurred in one patient. No grade 4 events or treatment-related deaths were reported. **Conclusions:** The combination of salvage SRS with Anlotinib demonstrated promising outcomes and manageable toxicity in managing recurrent GBM. Currently, a phase II randomized controlled trial, supported by the Shanghai Municipal Commission of Health, is underway. This trial aims to compare the efficacy of Anlotinib combined with radiosurgery against Bevacizumab combined with radiosurgery for the treatment of rGBM patients, further exploring this therapeutic regimen. Clinical trial information: NCT04197492. Research Sponsor: Shanghai Municipal Commission of Health and Family Planning; No. 20234Y0306.

Distribution and mutational landscape of inherited cancer susceptibility syndromes in central nervous system tumors.

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Background: Inherited cancer susceptibility syndromes (ICSS) caused approximately 5%–10% of malignancies. The fifth edition of the World Health Organization Classification of Tumors emphasized that central nervous system (CNS) tumors are associated with various ICSS. Our understanding of CNS tumors, both at the systemic and germline levels, has significantly improved with the increasing popularity of next-generation sequencing (NGS) testing. Recognizing individuals with ICSS in primary CNS tumors is crucial for optimizing proper genetic counseling and improving therapeutics and clinical care, and may further directly enhance patient outcomes. **Methods:** We retrospectively analyzed the ICSS of 4,828 patients with CNS tumors in a Chinese cohort, including age, cancer type, and sex distribution, and further investigated the somatic and germline mutations of cancer-related genes. Additionally, we examined the molecular characteristics of CNS tumors with ICSS and their clinical significance for diagnostic and therapeutic purposes. **Results:** Our study identified 258 (5.34%) patients with ICSS among 4,828 patients with CNS tumors with 265 germline P/LP variants, and identified 34 categories of ICSS, including 20 types of ICSS occurring in 28% (72/258) of patients not listed in the WHO CNS 5 classification. The gene with the highest germline P/LP mutation frequency was *TP53* (9.69%), followed by *MSH2* (9.30%), *NF1*(8.91%), and *BRCA2* (7.75%). These ICSS-associated genes were significantly enriched in the DNA repair and genomic stability signaling pathways (67%, 178/265). The two-hit events mainly focused on *NF1*, *MSH6*, and *MSH2*. The genes with the top five somatic mutation frequencies were *TP53* (42.25%), *TERT* (30.23%), *CDKN2A* (28.68%), *CDKN2B* (27.52%), and *PTEN* (25.58%). The top five ICSS in CNS tumors were Lynch syndrome, BRCA-related cancer predisposition syndrome, Li-Fraumeni syndrome, Fanconi anemia, and neurofibromatosis type 1. ICSS analysis reclassifies CNS tumors of "NOS" and 53.88% (139/258) of patients diagnosed with ICSS harboring potential precision oncology therapy target mutations. **Conclusions:** Our study is the first to include a large-scale cohort of patients with CNS tumors with ICSS and analyze the clinical and genomic features as well as their clinical significance. Results in our study of CNS tumors with ICSS are expected to improve disease entire process management, which is an important application of DNA-based NGS in ICSS evaluation and management and provides a reference direction for the future design of clinical trials. Research Sponsor: None.

Phase I clinical trial of ^{64}Cu-ATSM for malignant brain tumors.

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Background: Malignant brain tumors such as glioblastoma have poor prognosis. Current standard therapies such as surgery, radiotherapy, and chemotherapy were frequently insufficient. Hypoxic tissue microenvironments induced by rapid cellular growth within tumor lesions lead to treatment resistance. **Methods:** Eligible patients had a histological diagnosis of grade III/IV glioma, primary central nervous system malignant lymphoma (PCNSL), or grade II/III malignant meningioma based on the most recent pathological diagnosis prior to enrollment, or metastatic brain tumor based on clinical course or imaging. Diacetyl-bis(N^4-methylthiosemicarbazone) radiolabeled with Cu-64 (^{64}Cu-ATSM) was synthesized as described elsewhere. ^{64}Cu-ATSM was administered intravenously once a week for 4 weeks. Adverse events were assessed using the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0). The trial had a traditional single arm open-label 3 + 3 design with four ^{64}Cu-ATSM dose cohorts: 30, 60, 99, and 150 MBq/kg. The primary objective was to assess dose-limiting toxicity (DLT) and to determine the maximum tolerated dose (MTD) of ^{64}Cu-ATSM. Overall survival (OS), progression-free survival (PFS), pharmacokinetics, and ^{64}Cu-ATSM effective radiation dose were evaluated as secondary endpoints. **Results:** In total, 20 patients were registered at National Cancer Center Hospital or Kanagawa Cancer Center. Eighteen patients who received ^{64}Cu-ATSM were included in the primary analysis. None of the 3 patients at 30 MBq/kg, 1 of 6 patients at 60 MBq/kg, and 1 of 6 patients at 99 MBq/kg developed DLT (grade 3 lymphocytopenia). Two of 3 patients at 150 MBq/kg developed DLT (grade 4 lymphocytopenia). Therefore, additional patient recruitment was terminated. The MTD was considered to be 99 MBq/kg. No serious adverse events caused by ^{64}Cu-ATSM administration were not reported. Median OS was 29.4 months and 1-year OS was 76.6%. Median PFS was 3.8 months and 1-year PFS was 19.0%. ^{64}Cu-ATSM was rapidly distributed to body organs after intravenous administration and subsequently disappeared gradually. The liver (0.23 mSv/MBq) received relatively high doses, with an estimated effective dose of 0.037 mSv/MBq. **Conclusions:** Intravenous administration of ^{64}Cu-ATSM was feasible and well tolerated in patients with malignant brain tumors. The recommended dose for future trials is 99 MBq/kg. The initial efficacy outcomes obtained in this study warrant more clinical evaluation of this new treatment approach for brain tumors with no currently available treatment options. Clinical trial information: jRCT2091220362. Research Sponsor: Japan Agency for Medical Research and Development (AMED); 20ck0106567s0201.

Glioma monitoring via longitudinal intracranial cerebrospinal fluid cell-free DNA.

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Background: Current methods for glioma treatment response assessment are limited. This study aimed to assess the technical and clinical feasibility of molecular profiling using intracranial CSF from patients with gliomas during their disease course. **Methods:** Adults with gliomas were recruited for longitudinal intracranial CSF collection using 1) Ommaya reservoirs, from which CSF would be sampled on at least two separate occasions, or 2) CSF collection from other clinically indicated CSF access devices, such as ventriculoperitoneal (VP) shunts. Patients were followed until their last visit or present time for ongoing participants. For this initial cfDNA feasibility study, CSF was collected from Ommaya reservoirs in four patients and from an existing VP shunt in one patient. cfDNA was then extracted and analyzed using two sequencing platforms, PredicineCARE for cancer variant profiling and PredicineSCORE for low-pass whole genome sequencing (LP-WGS). This analysis generated genomic aberration profiles and genome-wide copy number burden (CNB) score. **Results:** Five patients (2 females, 3 males; median age: 40 years, range 32-64 years) underwent longitudinal intracranial CSF collection via Ommaya reservoirs (n=4) or VP shunt (n=1). In total, thirty-five CSF samples were obtained (median volume: 3.80 mL; 0.5-5 mL), with 30 samples (85.7%) yielding sufficient cfDNA for variant profiling and LP-WGS. Our initial findings suggest that tumor fraction increased by 6.28x and 2.87x with radiographic progression in two patients. Tumor fraction decreased by 0.08x and 0.04x in two patients with paired immediate pre-versus-post chemoradiation samples. Despite ongoing pseudoprogression in one patient, tumor fraction decreased to unmeasurable levels from a post-resection baseline of 0.26. Patient-specific tumor-associated variant allelic frequencies (VAFs), including TP53, PTEN, TERT, and CDKN2A/B, decreased within individual patients after resection and chemoradiation. In two patients with isocitrate dehydrogenase (IDH) mutant gliomas, decreasing IDH1 VAF after resection correlated with decreased CSF D-2-hydroxyglutarate (D-2-HG) levels (0.64x and 0.62x, respectively, for the first patient, and 0.01x and 0.07x for the other patient). Both CSF IDH1 VAF and CSF D-2-HG increased in the patient who had radiographic progression (2.56x and 9.21x, respectively). Moreover, CNB decreased below the limit of quantification during treatment and increased above the limit at progression. **Conclusions:** Longitudinal CSF cfDNA can feasibly be obtained via CSF access devices in patients with gliomas during their disease course. Ongoing studies will evaluate hypotheses generated in this case series regarding how longitudinal CSF cfDNA could be utilized to sensitively detect changes in disease burden. Clinical trial information: NCT04692337; NCT04692324. Research Sponsor: NIH NINDS; R61 NS122096.

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Phase 1 LITESPARK-001 study of belzutifan in advanced solid tumors: Results of the glioblastoma cohort.

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Background: Patients with progressive/recurrent glioblastoma (GBM) have very poor prognosis, and novel treatments are urgently needed. Hypoxia is a prominent feature of the tumor microenvironment in GBM and has been implicated as a potential mechanism of resistance to radiation therapy, which is a key part of standard-of-care treatment for GBM. HIF-2α has been suggested as a key therapeutic target because it plays a role in stabilizing the hypoxic environment in GBM tumors. Belzutifan, a first-in-class HIF-2α, has shown efficacy in advanced renal cell carcinoma and in von Hippel-Lindau disease–related renal cell carcinoma, pancreatic neuroendocrine tumors, and central nervous system hemangioblastomas. The phase 1 LITESPARK-001 trial (NCT02974738) was designed to evaluate belzutifan across solid tumors. Here, we report results from the GBM expansion cohort of LITESPARK-001. **Methods:** Patients enrolled in the GBM cohort had histologically confirmed, IDH wild type GBM that is first recurrent following radiation therapy and temozolomide according to the Response Assessment in Neuro-Oncology (RANO) criteria and had a measurable contrast-enhancing lesion by MRI imaging and a Karnofsky performance scale score $\geq$60%. Patients received belzutifan 120 mg by mouth twice daily. End points for this cohort included objective response rate (ORR), clinical benefit rate (CBR, CR + PR + SD of any duration), and progression-free survival (PFS) per RANO criteria by investigator assessment and safety. **Results:** Overall, 25 patients were enrolled in the GBM cohort. Median age was 63 years (range, 35-75), and most patients were male (n = 15; 60%). Median follow-up was of 1.9 months (range, 0.7-5.1). ORR was 0% (95% CI, 0.0-13.7) and CBR was 8% (95% CI, 1.0-26.0). Median PFS was 1.4 months (95% CI, 1.1-1.8). All patients (100%) experienced $\geq$1 adverse event and 15 (60%) experienced a grade 3-5 adverse event. The most common adverse events were anemia (n = 16 [64%]), fatigue (n = 13 [52%]), headache (n = 8 [32%]), muscular weakness (n = 8 [32%]). Two patients (8%) died from adverse events (both disease progression). No deaths were considered related to treatment. **Conclusions:** Antitumor activity was not observed with belzutifan for patients with GBM who received prior radiation therapy and temozolomide. The safety profile was similar to previous studies with belzutifan. Further efforts are warranted to identify therapies for patients with glioblastoma to improve outcomes. Clinical trial information: NCT02974738. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Cost-effectiveness of dabrafenib plus trametinib in BRAFV600E-mutant pediatric low-grade glioma: A microsimulation study.

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Background: BRAFV600E mutations, detected in 15-20% of pediatric low-grade gliomas (PLGGs), have emerged as a key therapeutic target for patients with unresectable, progressive, or recurrent PLGG. In a recent phase II clinical trial (NCT02684058), dabrafenib, a selective inhibitor targeting BRAFV600E, plus trametinib outperformed standard chemotherapy as first-line therapy, demonstrating significantly longer progression-free survival and improved safety in BRAFV600E-mutant PLGG. The aim of this study was to estimate the cost-effectiveness of dabrafenib+trametinib (Dab-Tram) versus standard chemotherapy as first-line therapy for patients with BRAFV600E-mutant PLGG. **Methods:** We constructed a micro-simulation model, simulating a cohort of 10,000 patients with BRAFV600E PLGG. We populated the model using progression-free and overall survival estimates derived from the NCT02684058 trial, a hospital-based PLGG registry and treatment- and PLGG-related adverse events from published literature. The simulated cohort was assigned to either targeted therapy or chemotherapy as first-line therapy. Key parameters included treatment cost, dosage, in-patient and outpatient costs, and health-related quality of life. We assumed a lifetime duration of targeted therapy, a healthcare system perspective, lifetime horizon, and discount rate of 1.5%. Outcomes included life years, quality-adjusted life years (QALYs), lifetime costs (2022 CAD), and incremental cost-effectiveness ratios (ICERs).Sensitivity analysis included the use of alternative data sources, including those derived from independent assessment of NCT02684058 trial outcomes and real-world data from The Hospital for Sick Children (Sick-Kids) in Toronto, Canada. **Results:** Modeled life years with Dab-Tram and chemotherapy were 34.91 and 32.68 years, respectively. Dab-Tram was associated with a 1.77 QALY increase at an incremental cost of $2,701,409 compared to standard chemotherapy. The resulting ICER was $1,526,265 per QALY gained. At a willingness-to-pay (WTP) threshold of $150,000 per QALY, a price reduction of approximately 80% is required to render it cost-effective. Scenario analysis varying effectiveness of targeted therapy using independent assessment of NCT02684058 trial outcomes and real-world data from SickKids demonstrated comparable clinical benefits and ICERs. Results were sensitive to changes in survival distributions. **Conclusions:** While clinical outcomes using Dab-Tram as first line therapy for BRAFV600E PLGG are promising, our model-based analysis demonstrates that at the present price, Dab-Tram is not cost-effective, and would require a considerable price reduction to enable equitable access and affordability. This work also provides an exemplar for economic evaluation of precision therapies based on emergent trial and real-world data for rare diseases. Research Sponsor: None.

A phase II, open label, single arm study of nivolumab for recurrent or progressive IDH mutant gliomas with prior exposure to alkylating agents.

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Background: Somatic mutations in isocitrate dehydrogenase 1 (IDH) are recognized as an important prognostic factor in patients with gliomas and are associated with longer survival. Regardless of initial grade, however, recurrence and transformation into higher grade tumors is almost universal. IDH-mutant gliomas are prone to develop hypermutation after exposure to alkylating agents; in other solid tumors, hypermutation may be a predictive biomarker for PD-1 inhibitor response. In this multicenter phase 2, open label, single arm study, we hypothesize that this specific subgroup of patients would demonstrate a clinically meaningful benefit from nivolumab as measured by overall response rate (ORR), duration of response (DOR), median progression-free survival (PFS), and overall survival (OS). **Methods:** Eligible patients aged 18 years and older with recurrent or progressive IDH-mutant (WHO Grades 2, 3, or 4) gliomas were included. All had prior exposure to alkylating agents. Nivolumab was given 240 mg q2w for 8 cycles, then 480 mg q4w until disease progression, unacceptable toxicity, withdrawal of consent, or completion of study at 2 years. Efficacy was evaluated by ORR of partial (PR) and complete responses (CR) based on RANO criteria; for patients with non-enhancing disease only, low-grade glioma RANO criteria was used. Secondary endpoints included median PFS and median OS, as well as DOR. Toxicity assessments continued for two safety monitoring follow-up visits off study. Survival follow-up occurred every 3 months until death or until study completion at 2 years. **Results:** Thirty-five patients were enrolled, with 33 (66.7% male) evaluable at study completion. Histology consisted of oligodendroglioma (N=11; 55% Grade 3) and astrocytoma (N=22; 36% Grade 3, 32% Grade 4). Median number of prior line of systemic therapy was 1 (range 1-6). Median dexamethasone dose at screening was 0 mg (range 0-4) and at end of study was 0 mg (range 0-8). ORR was 9% with two PR and one CR, with median DOR of 33 months. All three patients maintained response at 20+ (Grade 3 oligodendroglioma), 33+ (Grade 3 astrocytoma) and 51+ months (Grade 2 astrocytoma). 11 (33%) patients had stable disease (8 were stable for over 6 months) with median PFS of 2.2 months and median OS of 31 months. Nivolumab was well-tolerated with two treatment-related Grade 3 adverse events (lymphopenia and hypotension). One patient discontinued treatment due to Grade 2 transaminitis. **Conclusions:** Nivolumab was well-tolerated with no unexpected toxicity in this brain tumor population. Three patients derived a prolonged response and still continue on CR and PR after completing 24 months of planned treatment. This study provides data on single-agent PD-1 inhibition, which will serve as baseline efficacy data for ongoing and future combination immunotherapy trials with PD-1 inhibitors in recurrent IDH-mutant gliomas. Clinical trial information: NCT03557359. Research Sponsor: Bristol-Myers Squibb.

Initial results from phase I trial of a novel oncolytic adenovirus Ad-TD-nsIL12 in recurrent glioblastoma connecting to ventricular system.

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Background: Glioma is the most common primary central nervous system malignancy in adults, of which glioblastoma (GBM) accounts for more than 50% of the incidence and is the most aggressive subtype of glioma, with a median survival of about 15 months. Oncolytic virus emerges as a promising therapy for recurrent GBM (rGBM), but its safety and efficacy are not evaluated in patients with rGBM connecting to ventricular system. **Methods:** This is a dose-escalating trial to study the safety and efficacy of Ad-TD-nsIL12, a novel oncolytic adenovirus, in patients with rGBM connecting to the ventricular system. The assigned dose levels of Ad-TD-nsIL12 were $5x10^9$vp, $1x10^{10}$vp, and $5x10^{10}$vp. Adverse events (AEs) associated with the virus were graded using the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0), and Grade $\geq$ 3 AEs identified the dose-limiting toxicity (DLT). Tumor response was evaluated based on the Response Assessment in Neuro-Oncology (RANO) criteria. **Results:** Eight patients, aged from 45 to 71 years, were enrolled between December 2019 and September 2022, with treatment doses ranging from $5x10^9$ to $5x10^{10}$vp. Grade 3 seizure according to CTCAE occurred in two patients from Cohort 3 ($5x10^{10}$vp) after AD-TD-nsIL12 injection. Minimal adverse events were observed at a treatment dose of $1x10^{10}$ vp, even after multiple injections. Complete response (CR) was demonstrated in one patient, partial response (PR) in one patient, stable disease (SD) in four patients and progressive disease (PD) in two patients. Immunohistochemical staining showed higher infiltrations of $CD3^+$, $CD4^+$ and $CD8^+$ T cells and positivity of E1A and Hexon in virus post-treated tissues. Inflammation associated cytokines in the blood were not significantly elevated by Ad-TD-nsIL12. **Conclusions:** AD-TD-nsIL12 treatment was safe and effective in patients with rGBM and warrants examination in a phase II clinical study. Clinical trial information: ChiCTR2000032402. Research Sponsor: National Key R&D Program of China; 2019YFC1316104.

Zotiraciclib for newly diagnosed or recurrent glioblastoma: Updated outcome and biomarker analysis.

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Background: There has been little progress in the treatment of newly diagnosed glioblastoma in decades and standards of care for recurrent glioblastoma remain poorly defined. The multi-cyclin dependent kinase inhibitor Zotiraciclib (TG02) depletes short-lived survival proteins such as c-MYC and MCL-1 which are overexpressed in glioblastoma. The mode of action is thought to be specific inhibition of cyclin-dependent kinase (CDK) 9. **Methods:** EORTC 1608 was a three parallel group (A,B,C) phase Ib, non-randomized, multicenter study in isocitrate dehydrogenase wildtype newly diagnosed glioblastoma or anaplastic astrocytoma. In groups A and B, the maximum tolerated dose (MTD) of Zotiraciclib in elderly patients, in combination with radiotherapy alone (group A) or temozolomide alone (group B), stratified by O^6-methylguanine DNA methyltransferase promoter methylation status, were determined. In group C, we explored single agent activity of TG02 at first relapse with a primary endpoint of progression-free survival at 6 months (PFS-6). Tumor expression of CDK-9, c-MYC and MCL-1 was determined by immunohistochemistry. Tumor-related extracellular vesicles were quantified according to the minimal information for studies of extracellular vesicles 2018 (MISEV2018) guidelines. **Results:** Main toxicities of zotiraciclib were neutropenia, gastrointestinal disorders and hepatotoxicity. The MTD was 150 mg twice weekly in group A (weekly) or twice weekly in alternating weeks in group B. PFS-6 in group C was 6.7%. The tumor expression of c-MYC and MCL-1 was moderately cross-correlated. High protein levels of MCL-1 were associated with inferior survival. The levels of tumor-related extracellular vesicles in the blood correlated with tumor volumes determined by MRI and increased from baseline to recurrence. **Conclusions:** Zotiraciclib exhibits overlapping toxicity with alkylating agents which are the cornerstone of medical treatment for glioblastoma. Its single agent clinical activity in the recurrent setting was low. The role of c-MYC and MCL-1 as therapeutic targets and the diagnostic value of extracellular vesicles in peripheral blood in glioblastoma warrant further study. Research Sponsor: This study was supported by a research grant from Adastra Pharmaceuticals and Cothera Bioscience (USA) to the European Organisation for Research and Treatment of Cancer (EORTC).

Phase IIb randomized, blinded, controlled trial evaluating neoadjuvant PD-1 blockade combined with A2B5$^+$ glioma stem-like cell lysate-loaded DC vaccine in recurrent glioblastoma (IDH1/2 -).

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Background: Our previous study showed A2B5$^+$ glioma stem-like cell lysate-loaded DC vaccine (GSC-DCV) extended survival in recurrent GBM. Additionally, our earlier research indicates that A2B5$^+$ GSCs, enriched with tumor-specific antigens like URGCP, have the potential to activate CD8$^+$ T cells via dendritic cell antigen presentation. Recent research on recurrent GBM suggest aPD-1 mAb neoadjuvant therapy further extends survival. This study is intended to assess the safety and efficacy of this combined therapeutic approach. **Methods:** Patients with recurrent GBM (IDH1/2 -) post-radiotherapy and chemotherapy were enrolled. All patients received aPD-1 mAbs before surgery. Post-surgery, patients were randomly assigned to the monotherapy arm (aPD-1 mAbs and placebo) or combination therapy arm (aPD-1 mAbs and GSC-DCV), with treatments given every 3-6 weeks until disease progression or intolerable toxicity. The primary endpoint was OS, and secondary endpoints included PFS and trAEs. **Results:** A total of 21 patients were randomly assigned to the monotherapy (n=11) and combination therapy (n=10) arms. Patient characteristics were well-balanced. The monotherapy arm had a median OS of 8.2 months, while the combination arm showed a significantly longer OS of 22.7 months (HR, 0.2774; 95% CI, 0.0828 to 0.9291, P=0.0376). Multivariate Cox model analysis confirmed the independent prognostic impact of the combination therapy on patients with recurrent GBM (HR, 9.911; 95% CI, 1.520 to 64.623; P=0.016). There was no statistically significant difference in PFS between the two arms. Notably, patients in the combination group experienced a substantial improvement in post-progression survival (PPS) compared to the monotherapy group (7.8 m vs. 1.4 m; P=0.0266). The long survival benefit observed in the combination group was associated with continuous treatment, as cessation led to short-term tumor progression. Subgroup analysis based on tumor burden revealed that the combination therapy was significantly more effective in the low tumor burden cohort (mOS: 23.2 vs. 9.6 months; P=0.0162). No significant difference was observed in the monotherapy group between the two cohorts. High URGCP expression was significantly positively associated with OS in patients undergoing combination therapy (R_2=0.8608, P=0.0061). Grade 1-2 trAEs were reported in 27.3% of patients in the monotherapy arm and 50.0% in the combination therapy arm. No grade 3 or higher trAEs occurred. **Conclusions:** The combination therapy has proven to be safe and well-tolerated. Although there was no significant improvement in PFS, patients achieved a sufficiently long OS benefit compared to the monotherapy arm. Notably, the combination therapy was particularly effective in patients with a low tumor burden through long-term, multi-course treatment. Clinical trial information: NCT04888611. Research Sponsor: National Key R&D Program of China grant 2022YFC3401600.

Development and validation of a clinical risk score for postoperative outcome in newly diagnosed glioblastoma: A report of the RANO Resect group.

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Background: Following resection or biopsy, patients with newly diagnosed glioblastoma frequently enter clinical trials. To standardize terminology for extent of resection, we proposed the RANO classification acknowledging four prognostic resection classes reflecting different amounts of residual tumor. Here, we aim to make use of our classification to (I) analyze the interactive effects of residual tumor with clinical and molecular factors on outcome (II) to define a prognostic postoperative risk score. **Methods:** The RANO *resect* group retrospectively compiled an international, seven-center training cohort of newly diagnosed glioblastoma. Predictors of outcome were identified by uni- and multivariate Cox's proportional hazard regression. The combined effects of residual tumor with prognostic molecular and clinical factors on survival were assessed by recursive partitioning analysis (significance level: $p \leq 0.05$). Terminal regression tree nodes were combined into risk classes guided by Kaplan-Meier survival analyses and log-rank tests. The risk classes were converted into a numerical score which was prognostically verified in an external validation cohort. **Results:** Our training cohort compromised 1003 patients with newly diagnosed *IDH*-wildtype glioblastoma, including 744 patients who underwent adjuvant radiochemotherapy per EORTC-NCIC (TMZ/RT→TMZ). Residual tumor per RANO classification, MGMT promotor methylation status, age (as continuous variable; optimal cutoff: ≤65 years), and KPS (as continuous variable; optimal cutoff: ≥80) were prognostic of overall survival and forwarded into regression tree analysis. By combining eleven terminal nodes and individually weighting the prognostic factors, an additive scale (range, 0-9 points) integrating these four variables distinguished patients with low (0-2 points), intermediate (3-5 points), and high risk (6-9 points) for poor postoperative outcome (median overall survival: 24 *vs.* 16 *vs.* 6 months; $p < 0.01$). Adjustment of the regression tree for adjuvant therapy was applied, and the presence of the three risk groups was confirmed in the subgroups of patients treated with or without RT/TMZ→TMZ. The prognostic value of the risk score was verified in a external single-center validation cohort of newly diagnosed glioblastoma ($n = 231$, $p < 0.01$). When we compared our risk score to previously postulated risk models, our score was superior in concordance between predicted with observed survival (c-index; development cohort: 0.7, validation cohorts: 0.6). **Conclusions:** The novel RANO risk score integrates molecular and clinical factors to serve as an easy-to-use, yet highly prognostic tool to stratify patients after resection or biopsy of newly diagnosed glioblastoma. The score may serve to guide patient management and reduce imbalances between study arms in prospective interventional trials. Research Sponsor: None.

2061 Poster Session

Primary intracranial germ cell tumors in adolescents and adults: Results of an international, multicenter, retrospective cohort study.

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Background: Primary Intracranial Germ Cell Tumors (iGCT) are rare. Previous prospective and retrospective studies mainly included pediatric patients (pts) with a median age of 10-14 years. The aim of this retrospective analysis was to evaluate characteristics, treatment and outcome of adolescents and adults with iGCT. **Methods:** Data were collected from 10 institutions in Germany and Switzerland. Pts aged >/= 16 years at first diagnosis or at relapse with a primary iGCT were included. Objective responses were evaluated by local investigators. Statistics (Cox proportional hazard model, progression-free survival (PFS) and overall survival (OS) analyzed by Kaplan-Meier method) were performed with SPSS v29. **Results:** We identified 75 pts (92.0% male) with a median age of 23 years (range 16-60, 94.7% >/= 18 years). At first diagnosis, histology was pure germinoma in 70.7%, pure teratoma in 10.7%, other non-germinomatous GCT (NGGCT) in 13.3%, unknown in 5.3% of pts. Localized, bifocal, and metastatic disease was found in 72.0, 6.7, and 21.3% of pts. As part of their first line (1L) treatment, 69.3%, 80.0%, and 62.7% received surgery, radiotherapy, and chemotherapy, respectively. High dose chemotherapy/ autologous stem cell transplantation (HDCT/ASCT) was part of 1L treatment in n=3 pts with NGGCT. Trimodal and bimodal treatment was performed in 48.0% and 32.0% of pts. Response to 1L therapy was complete remission (CR) in 61.3%, partial remission tumor marker negative (PRm-) in 16.0%, PRm+ in 4.0%, PR with tumor marker status unknown in 4.0%, progressive disease (PD) in 2.7%, and unknown in 12.0%. Relapse occurred in 13/75 pts (17.3%) with unknown histology (n=4), teratoma (n=2), other NGGCT (n=4), and germinoma (n=3). In 2 pts. in whom germinoma was diagnosed at time of first diagnosis, at time of recurrence PNET and Yolk sac tumor were histologically proven. Median time to relapse was 19.0 months (mo.; range 3-223). HDCT/ASCT as salvage treatment was performed in 5 pts with NGGCT and in one pt with germinoma as 2L (n=5) or 3L (n=1). NGGCT histology was associated with increased risk for recurrence or death (p=0.012 and 0.039).3-year PFS was 90.7% (germinoma: 98.1%, NGGCT: 73.9%) and 5-year OS was 92.0% (germinoma: 98.1%; NGGCT: 78.3%). Median follow-up time was 60 mo (range 0-339). **Conclusions:** Disease characteristics, treatment and outcomes of adolescent/ adult iGCT pts are comparable to those reported in pediatric pts. High cure rates are achieved in pts with pure germinoma and current treatment concepts. In pts with NGGCT further investigation is needed to improve survival outcomes. Research Sponsor: None.

Safety and efficacy of B7-H3 targeting CAR-T cell therapy for patients with recurrent GBM.

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Background: Glioblastoma Multiforme (GBM) is one of the most deadly cancers, and nearly all patients experience recurrence upon the current standard of care for newly diagnosed GBM. The recurrent GBM (rGBM) exhibits a median survival of less than 8 months with limited therapeutic options. We have previously cloned the B7-H3 gene, characterized its function, demonstrated altered B7-H3 expression in human solid tumors, and identified B7-H3 as a promising therapeutic target. We present herein the preliminary findings of an investigator-initiated trial (NCT05241392), where patients with rGBM were treated with autologous chimeric antigen receptor-T (CAR-T) cells targeting B7-H3 (TX103). **Methods:** This is an open, single-arm, "3+3" dose-escalation and multiple-dose study. The primary objective was to evaluate the safety and the maximal-tolerated dose. Secondary objectives included survival outcomes, tumor responses, immunological responses, and pharmacokinetic parameters. Patients aged 18 to 75 were enrolled with confirmed recurrence by image scan and B7-H3 expression >= 30% by immunohistochemistry analysis. TX103 was administered intracavity and/or intraventricularly to patients via an Ommaya reservoir. TX103 was given biweekly to patients each cycle at dose levels 1, 2, and 3 (20, 60, 150 million cells, respectively), with four cycles as one course. **Results:** Between March 2022 and January 2024, 13 patients received at least one intracranial infusion of TX103, with 3, 4, and 6 patients in dose levels 1, 2, and 3, respectively. The median number of infusion cycles was 4 (Min, Max 1,9). All patients were included in the safety analysis, revealing no dose-limiting toxicity or CAR-T treatment-related death. All patients experienced at least one adverse event (AE), and the treatment-related AEs (TRAEs) included cytokine release syndrome, increased intracranial pressure (ICP), headache, epilepsy, decreased level of consciousness, vomiting, and pyrexia. Most TRAEs were grade 1-2, while three grade-3 TRAEs were observed: one case of increased ICP in dose level 2, one case of epilepsy, and another case of decreased level of consciousness in dose level 3. As of January 2024, six patients from dose levels 1 and 2 were eligible for a 12-month survival assessment; the 12-month overall survival (OS) rate was 83.3% (95% CI: 58.3%~100%), and the median OS was 20.3 mo (95% CI: 20.3~not reach). Two of the three patients from dose level 2 achieved partial and complete responses, respectively. Following CAR-T administration, significant increases in cytokines, including IL-6 and IFN-γ, and elevated copy numbers of the CAR gene were observed in the cerebrospinal fluid, while only minimal elevations were noted in the peripheral blood. **Conclusions:** In this trial, treating rGBM with TX103 is deemed safe and tolerated. These interim results support further study using TX103 to enhance the survival outcomes in patients with rGBM. Research Sponsor: Fuzhou Tcelltech Biological Science and Technology Inc.

Multi-institutional study of reirradiation for recurrent high grade glioma.

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Background: Treatment options are limited for recurrent WHO Grade 3-4 glioma (HGG). Reirradiation (ReRT) is an option, but the ideal treatment regimen and the benefit of concurrent and adjuvant systemic therapy in the recurrent setting remains unclear. **Methods:** A retrospective review of patients with recurrent HGG treated with reRT was conducted at 12 institutions. Eligible patients were treated with two courses of fractionated RT (>3 fractions) for glioma with the second course being for HGG. To estimate overall and progression free survival times, the Kaplan-Meier method was used. To assess the relationship between survival times and study variables, Cox proportional hazard regression models were used to calculate hazard ratios and the corresponding 95% confidence interval along with the p-value. SAS (version 9.4, Cary, NC, USA) was used for all analyses. P values < 0.05 were assumed to be statistically significant. **Results:** 482 eligible patients were identified from 1997 to 2023. 235 (54%) had histologic confirmation of glioblastoma at reRT. The median age at reRT was 53.1 years and median KPS was 80. 196 patients (51%) were treated with reRT at their initial recurrence and 122 (30%) had an IDH mutation. The most common reRT dose and number of fractions were 35 Gy and 10 fractions. 192 patients (44%) and 95 (24%) received concurrent (conc) and adjuvant (adj) temozolomide (TMZ) respectively and 116 (27%) and 110 (28%) received conc and adj bevacizumab (BEV) respectively with reRT. Median OS and PFS were 9.8 and 5.3 months. OS (16.6 vs 7.8 months, HR 2.44 $p < 0.01$) and PFS (8.6 vs 4.6 months, HR 1.85 $p < 0.01$) were longer in patients with IDH mutations. Receipt of conc and adj TMZ with reRT was associated with improved OS (HR 0.67 $p < 0.01$ and HR 0.49 $p < 0.01$ respectively) and PFS (HR 0.66 $p < 0.01$ and HR 0.47 $p < 0.01$ respectively). Receipt of concBEV with reRT was associated with worse OS (HR 1.66 $p < 0.01$) but not PFS (HR 1.15 $p = 0.28$). AdjBEV was not associated with OS or PFS. Concurrent and adjTMZ were associated with improved OS ($p = 0.04$ and <0.01) and PFS ($p = 0.01$ and <0.01) for IDHwt tumors. In IDHmt tumors, concTMZ was associated with improved OS but not PFS ($p = 0.03$ and 0.11), while adjTMZ was associated with improved OS and PFS ($p = 0.05$ and <0.01). Symptomatic adverse radiation effects and Grade 3 or greater neurologic toxicity were seen in 107 (25%) and 86 (20%) of patients respectively. Neither conc nor adjBEV nor TMZ were associated with symptomatic ARE. ConcBEV was associated with lower (13% vs 23%, $p = 0.03$) and concTMZ was associated with higher rates (25% vs 15%, $p = 0.01$) of Grade 3 or greater neurologic toxicity. **Conclusions:** The use of concurrent and adjuvant TMZ with reRT are associated with improved OS and PFS in recurrent HGG. OS and PFS are improved with conc and adjTMZ for IDHwt tumors, while there was no PFS benefit to concTMZ in IDHmt tumors. The rate of high grade neurologic toxicity was decreased with the use of concurrent BEV and increased with the use of concTMZ. Research Sponsor: National Center for Advancing Translational Sciences (NCATS), National Institutes of Health funded Wake Forest Clinical and Translation Science Institute (WF CTSI); UL1TR001420.

LBA2064 **Poster Session**

VAMANA: A phase 2 study of low-dose bevacizumab plus CCNU in relapsed/recurrent glioblastoma.

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Enrichment of glioblastoma tumor microenvironment in a GZMK+ T cell population.

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Background: Glioblastoma (GBM) bears a survival estimate below 10% at 5 years, despite standard chemoradiation treatment. Trials evaluating immune checkpoint blockade (ICB) in gliomas have been disappointing so far, dealing with the unique immunosuppressive tumor microenvironment (TME) of the brain. Nevertheless, we have clinical evidence of ICB efficacy for brain metastases (BrM) of immunosensitive tumors. Even if both GBMs and BrM share the same organ-specific microenvironment, it is clear that disease-specific immune characteristics instruct differential response to ICB. **Methods:** By using advanced deep learning algorithms to combine public and in-house-generated single-cell RNA sequencing profiles, we analyzed immune infiltrate characteristics of 602949 CD45+ cells from 76 GBM, 30 BrM from different types of extracranial tumors (13 NSCLC, 12 melanoma, 2 ovarian, 1 breast, 1 colorectal and 1 renal carcinoma) and 3 normal brain samples. The analysis was restricted to newly diagnosed GBM, excluding recurrent and pre-treated cases. CD8+ cells underwent segregation into clusters based on log2 normalized expression levels of CD3E and CD8A (with expression values greater than 0). The data integration utilized DESC, a deep learning model founded on autoencoders, and subsequent examination was conducted within the Scanpy framework. Cluster analysis was executed employing the Leiden algorithm. Differentially expressed genes (DEGs) were pinpointed across clusters using the Wilcoxon test, with False Discovery Rate (FDR) correction carried out through the Benjamini-Hochberg procedure. **Results:** From CD45+CD3+ cells, we isolated CD8+ T cells and identified 7 informative CD8+ T cells clusters. Based on DEGs, we could appreciate T cells clusters that were also recapitulated in other extracranial malignancies. The most abundant subset was composed of *GZMK*+ effector T cells (Cluster 0: *GZMK*, *GZMM*, *CD44*, *KLRG1*, *IL7R*, *GZMA*, *CXCR3*), followed by putative tumor-specific tissue-resident memory cells (Cluster 1: *GZMB*, *LAG3*, *CTLA4*, *TIGIT*, *CXCL13*, *ITGAE*, *ENTPD1*, *PDCD1*, *CD27*, *HLA-DRB1*), stem-cell memory-like T cells (Cluster 3: *IL7R*, *CCR7*, *JUNB*, *KLF2*, *TCF7*) and a less represented cluster characterized by high expression of genes belonging to the HSP family (Cluster 4: *HSPA1*, *HSPH1*, *HSPE1*, *HSPD1*, *IFN*). Interestingly, while the majority of the identified clusters was equally represented in the 3 different tissues, the *GZMK*+ effector T cells cluster (Cluster 0) was found to be more represented in GBM compared to BrM and normal brain tissue. **Conclusions:** A *GZMK*+ effector T cells subpopulation, specifically enriched in GBM, has been poorly characterized in its function and spatial localization. Our data highlight the importance of studying the composition of the immune infiltrate in GBM with multi-omics approaches in order to uncover deep mechanisms of resistance to ICB and eventually provide hints on potential therapeutic targets.
Research Sponsor: None.

Deciphering pediatric low-grade glioma trajectories: Deep learning–based volumetrics for patients under surveillance.

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Background: Pediatric low-grade gliomas (pLGGs) have heterogeneous clinical presentations and prognoses. Given the morbidity of treatment, some suspected pLGGs, especially those found incidentally, are surveilled without treatment, though the natural histories of these tumors have yet to be systematically studied. We leveraged deep learning and multi-institutional data to methodically analyze longitudinal volumetric trajectories of pLGGs on surveillance, yielding insights into their growth trajectories and clinical implications. **Methods:** We conducted a pooled, retrospective study of pLGG patients diagnosed between 1992 and 2020 from two sources (Dana-Farber Cancer Institute/Boston Children's Hospital and the Children's Brain Tumor Network), who were surveilled untreated for at least one-year post-diagnosis and who had linked clinical data and longitudinal MRI available. We applied a validated pLGG deep learning segmentation algorithm to longitudinal T2-weighted MRIs and calculated the 3-dimensional volumes at each timepoint. We evaluated individual tumor trajectories, curve shape, treatment initiation, and risk factors such as age, sex or tumor location for radiographic progression and regression (defined as volumetric change >=25% and <=-25% respectively) with univariable and multivariable logistic regression. Unsupervised time-series K-means and density-based spatial clustering with dynamic time wrapping were conducted to uncover volumetric phenotypes and a hybrid statistical time-series algorithm combining auto-regressive integrated moving average and generalized autoregressive conditional heteroskedasticity was evaluated to predict future volumetric changes. **Results:** Of 1774 scans from 129 patients (median follow-up of 4.0 years and median age of 13.9 years), baseline tumor median volume was 5.8 cm^3 (range: 0.01-108.1), with 33 cortical (25.5%), 21 brainstem (16.2%), and 21 (16.2%) cerebellar locations. At the last follow-up, 33.8% of tumors progressed, 35.8% were stable, and 30.2% had regressed. Treatment was initiated for 46.5% of the tumors, of which 70.4% underwent surgery. Risk factors such as adolescent age, larger baseline volume size, cortical location and symptomatic presentation were most associated with progression ($p<0.05$ for each). Clustering revealed three distinct volumetric phenotypes with diverging natural histories, corresponding to progression, stability or regression. The hybrid forecasting showed average root-mean-squared error values of >1 cm^3 (std. >0.18 cm^3) at training and testing combined. **Conclusions:** Deep learning auto-segmentation enables longitudinal, volumetric tracking of pLGG, yielding novel insights into the clinical trajectories of untreated tumors on surveillance, allowing a classification into progressors, regressors and stables. Research Sponsor: None.

Interim report of a phase 2 study of sonodynamic therapy (SDT) using SONALA-001 together with MR-guided low-intensity focused ultrasound (MRgFUS) in children with diffuse intrinsic pontine glioma (DIPG).

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Background: Children with DIPG have limited treatment options and a poor prognosis, with median survival of 9-12 months. Preclinical studies reveal that sonodynamic therapy (SDT) with MR-guided focused ultrasound (MRgFUS) activates ALA metabolite, protoporphyrin IX (PpIX), leading to tumor cell death and extending survival in glioma models. **Methods:** SDT-201 (NCT05123534) is a multi-center, first-in-child dose escalation trial of SDT with SONALA-001 and MRgFUS administered in children aged $\geq$ 5 years with DIPG, enrolled 4-20 weeks post-radiation therapy and prior to disease progression. The trial evaluates the safety and preliminary efficacy of SDT and pharmacokinetics (PK) of intravenous ALA (SONALA-001) at 5mg/kg, administered 6-12 hours before MRgFUS to the pons (delivered to half the pons 30 days apart for the first patient in each cohort of 3, with subsequent patients receiving entire pons treatment). The trial was subsequently amended to allow up to 12 monthly treatments. **Results:** Six patients in 2 cohorts were treated (4 male:2 female, range 5-12 years) between August 2022 and December 2023. No DLTs or related AE grade $\geq$ 3 were observed. For SONALA-001, the C_{max} occurred at the end of infusion, followed by rapid clearance (15.7 mL/min/kg) with plasma half-life of $<$ 1 hour, indicating rapid distribution. The PpIX C_{max} occurred 4-6 hours post-dose and declined with a longer mean half-life than SONALA-001 of 6 hours. Both C_{max} and AUC_{all} demonstrate circulating-PpIX and systemic exposure were significantly lower than for SONALA-001. Two of the first 6 patients achieved a partial response per RAPNO central-review, and 2 subjects continuing treatment are 11 to 15 months from start of study therapy. **Conclusions:** SDT is a well-tolerated strategy for patients with DIPG after initial radiotherapy. SONALA-001 shows rapid distribution and clearance, and PpIX PK align with metabolite formation. Following dose escalation completion, dose-expansion will be initiated at RP2D offering further insights into safety, PK, and efficacy. Clinical trial information: NCT05123534. Research Sponsor: None.

Phase 1 study of BDTX-1535, an oral 4th generation covalent EGFR inhibitor, in patients with recurrent glioblastoma: Preliminary dose escalation results.

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Background: Epidermal growth factor receptor (*EGFR*) gene is the most frequently altered oncogenic driver in glioblastoma (GBM). In-frame deletion alterations (e.g., EGFRvIII) and missense mutations co-occur in the setting of *EGFR* gene amplification and are characterized as a hallmark of disease pathogenesis in GBM. BDTX-1535 is an oral, highly potent, brain penetrant, selective, irreversible 4^{th} generation tyrosine kinase inhibitor that targets EGFR alterations in GBM and NSCLC. Preliminary results of the Phase 1 dose escalation study (NCT05256290) of patients with recurrent GBM (rGBM) are presented here. **Methods:** BDTX-1535-101 is a first-in-human study that enrolled patients with either rGBM harboring EGFR alterations following standard of care or patients with locally advanced or metastatic EGFR mutated NSCLC that progressed on prior EGFR TKIs. Using an adaptive Bayesian optimal interval design in the Phase 1 part, patients were enrolled at increasing dose cohorts and were treated daily for 21-day cycles until treatment discontinuation. The primary objective was to determine the BDTX-1535 recommended Phase 2 dose based on the overall safety, PK, pharmacodynamics, and preliminary antitumor activity. **Results:** Twenty-seven patients with rGBM were enrolled in the Phase 1 cohort that consisted of 54 patients in total including 27 patients with NSCLC. Patients were treated across seven dose levels (15mg – 400mg QD). The mean age of patients with rGBM was 58.7 years (range 41-85) with 96% of patients with previous temozolomide (TMZ) treatment and a median of 2 lines of prior therapy (range 1-4). The most common all-grade treatment-related AEs across all cohorts were rash (78%), diarrhea (41%), fatigue (15%), stomatitis (11%), decreased appetite (11%), nausea (11%) and paronychia (11%). Gr 3 TRAEs $\geq$ 10% included rash (19%) reported at 300 or 400 mg QD doses. Plasma exposure of BDTX-1535 increased dose proportionally and had a half-life of ~15h, supporting once daily dosing. The maximum tolerated dose (MTD) is 300 mg QD. Among 19 evaluable patients for response based on RANO criteria, 1 confirmed partial response was observed and 8 patients achieved stable disease. Five patients remained on BDTX-1535 with stable disease for an extended period (>5 months) who previously performed poorly on TMZ with short treatment duration, and 1 patient continues on BDTX-1535 after 16 months of treatment. **Conclusions:** BDTX-1535 was well-tolerated up to 300mg daily, which is the MTD, and promising preliminary clinical activity was observed in patients with rGBM after relapse on standard of care treatment. Given the inability to reconfirm EGFR status at the time of treatment with BDTX-1535 in this Phase 1 trial, further exploration of BDTX-1535 in a "window of opportunity" study is ongoing (NCT06072586). Clinical trial information: NCT05256290. Research Sponsor: Black Diamond Therapeutics.

A phase 0/1 trigger trial of BDTX-1535 in patients with recurrent high-grade glioma (HGG) with EGFR alterations or fusions.

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Background: This Phase 0/1 clinical trial evaluates the pharmacokinetic (PK), pharmacodynamic (PD), and clinical response of recurrent high-grade glioma (HGG) patients with EGFR alterations and/or fusions to the ATP-competitive, irreversible EGFR inhibitor, BDTX-1535. **Methods:** Recurrent HGG patients with EGFR alterations (Arm A) or EGFR fusions (Arm B) received 5 days of BDTX-1535 (200 mg) prior to planned resection at 2-4 hours following the final dose. In the Phase 0 component of the study, total and unbound drug concentrations were measured in tumor tissue (Gadolinium enhancing and non-enhancing regions), cerebrospinal fluid (CSF), and plasma using validated LC-MS/MS methods. A PK 'trigger', defined as unbound drug concentration above 5-fold biochemical IC50 in Gadolinium (Gd)-nonenhancing tumor, determined eligibility for Phase 1. PD response was assessed by quantification of percentage of positive pEGFR, pERK and MIB-1 cells in the surgical tumor tissue compared to baseline pre-treatment tissue. Patients with tumors exceeding the PK threshold for unbound drug concentration were eligible for expansion phase therapeutic dosing of BDTX-1535. **Results:** A total of 7 patients with recurrent glioblastoma (Arm A) were enrolled in the Phase 0 component of the study. Two patients were excluded from PK analysis due to pseudoprogression. The mean unbound concentrations of BDTX-1535 in Gd-enhancing and nonenhancing tumor regions were 16.0 nM and 10.5 nM respectively. Four of five (80%) evaluable patients exceeded the PK threshold. The suppression of pEGFR and MIB1 was observed in 40% and 60% of patients, respectively. No serious adverse events were observed among patients in the Phase 1 component of the study and a clinical readout is planned in Q2 2024. **Conclusions:** BDTX-1535 is well-tolerated in recurrent HGG patients, achieves pharmacologically relevant concentrations in Gd-nonenhancing tumor tissue and is associated with suppression of EGFR signaling. Clinical trial information: NCT06072586. Research Sponsor: Ben and Catherine Ivy Foundation & Barrow Neurological Foundation.

PK-PD-efficacy modeling of brigimadlin in *MDM2*-amplified glioblastoma.

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Background: Brigimadlin (BI 907828) is a potent small molecule inhibitor of the p53-MDM2 pathway currently in a phase 0/1 clinical trial in combination with radiotherapy in newly diagnosed *MGMT*unmethylated glioblastoma (GBM). To inform development of brigimadlin for GBM, we developed a pharmacokinetic (PK)/ pharmacodynamic (PD)/ efficacy model using GBM patient derived xenografts (PDXs). **Methods:** Brigimadlin PK parameters were evaluated in FVB wild-type and knockout (Mdr1a/b$^{-/-}$Bcrp1$^{-/-}$) mice and in athymic nude mice. Drug binding was measured by rapid equilibrium dialysis, and drug levels quantified by LC/MS-MS. Dose-response relationships were evaluated in subcutaneous and orthotopic PDXs across a range of doses. Response to brigimadlin (2 mg/kg weekly) +/- RT (2 Gy x 10 fractions) was evaluated in orthotopic PDXs. **Results:** Brigimadlin significantly delayed median time to regrowth of GBM108 (*MDM2*amplified) subcutaneous tumors (vs. placebo; $p<0.05$) at dose levels of 0.25 mg/kg (1.3-fold), 0.5 mg/kg (1.5-fold), 1 mg/kg (2.6-fold), and 2 mg/kg (5.3-fold). A single dose of brigimadlin resulted in corresponding intra-tumoral drug levels 24 hours post-dose: 84 nM (0.25 mg/kg), 175 nM (0.5 mg/kg), 398 nM (1 mg/kg) and 924 nM (2 mg/kg) and dose-dependent upregulation of p53 target genes (p21 and PUMA). In contrast, GBM14 (*MDM2*non-amplified) showed regrowth delay (1.6-fold) only at 2 mg/kg (p=0.008). Brigimadlin was highly bound (fraction unbound = 0.0006 in brain; 0.0017 in GBM tumor tissue), and CNS distribution was limited by efflux; in wild-type mice Kp,uu_brain = 0.002 ± 0.003; in Mdr1a/b$^{-/-}$Bcrp1$^{-/-}$ mice Kp,uu = 0.043 ± 0.025. Efficacy of brigimadlin was compared in orthotopic GBM108 PDXs grown in athymic nude mice vs. immuno/efflux-deficient (Rag2$^{-/-}$ Mdr1a$^{-/-}$Bcrp1$^{-/-}$) mice. In nude mice, median survival was extended at 2 mg/kg brigimadlin (1.4-fold, p=0.009), with corresponding intra-tumoral drug levels of 29 nM. In efflux deficient mice, median survival was extended ($p<0.05$) at 0.25 mg/kg (1.5-fold), 0.5 mg/kg (1.5-fold), 1 mg/kg (1.8-fold), and 2 mg/kg (>4-fold). Measurement of intra-tumoral drug levels is in progress. In combination with RT in GBM108, brigimadlin (2 mg/kg x 2 weeks) extended median survival vs. vehicle (66 vs. 50 days; p=0.012) and enhanced median survival following RT (128.5 vs. 82 days; p=0.009). In GBM14, 2 mg/kg brigimadlin (2 mg/kg x 12 weeks) extended median survival (39.5 vs. 32.5 days; p=0.0004) and enhanced survival following RT (97 vs. 81 days; $p<0.0001$). **Conclusions:** Efficacy of brigimadlin is dependent on adequate CNS delivery. Studies in subcutaneous PDX demonstrated intra-tumoral total drug levels in the mid-nanomolar range provide meaningful tumor effects in a highly sensitive, *MDM2* amplified PDX. In orthotopic PDXs with and without *MDM2* amplification, brigimadlin provided further benefit in combination with RT. These data support ongoing clinical evaluation of brigimadlin in GBM.
Research Sponsor: U.S. National Institutes of Health; U19CA264362; Mayo Clinic; Boehringer Ingelheim.

A randomized, controlled, phase 2 trial of nivolumab plus standard-dose or low-dose bevacizumab for recurrent glioblastoma (NAVAL).

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Background: PD-1/PD-L1 inhibition has demonstrated limited efficacy for recurrent glioblastoma (rGBM) across prior RCTs. VEGF, a proangiogenic factor upregulated in rGBM, contributes to tumor-associated immunosuppression. Preclinical and observational clinical data indicate a potential dose-dependent effect of anti-VEGF therapy on immune response. This RCT evaluated anti-PD-1 plus anti-VEGF therapy for rGBM. **Methods:** NAVAL was a multicenter, open label, phase 2 RCT that enrolled 90 patients (≥18 years) with GBM at first recurrence. Participants received nivolumab (240 mg IV Q2 weeks), and were 1:1 randomized to concurrent 10 mg/kg bevacizumab (*standard-dose arm*) or 3 mg/kg bevacizumab (*low-dose arm*) administered IV biweekly. Stratification factors included age, performance status, extent of resection, and MGMT methylation status. Primary endpoint was overall survival (OS) at 12 months (OS-12). Other outcomes were overall objective response rate (ORR), median progression-free survival (PFS), PFS at 6 months (PFS-6), and safety. Exploratory genomic and immune profiling using CITEseq was performed in 16 patients. **Results:** 90 patients were enrolled with median age of 60.6 years (range 27-86). 35 patients were MGMT methylated, 53 were unmethylated and 2 were indeterminate. Final analysis had 87 evaluable patients, with median follow-up of 146 days (range 7-1239). There were 3 complete responses (3.4%), 29 partial responses (33.3%), 37 stable disease (42.5%), and 18 progressive disease (20.7%). OS-12 was 41.1% and 37.7% in standard-dose and low-dose arms respectively, with PFS and ORR data in table. Post-hoc analysis demonstrated survival benefit for patients aged ≥60 years in standard-dose arm. Most frequent toxicities (>20%) included fatigue (45.6%), proteinuria (34.4 %), diarrhea (28.9%), hypertension (23.3%) and lipase increase (21.1%). Grade 3-4 toxicities included hypertension (7.8%), fatigue (5.6) and non-neurological toxicities. Differential changes across trial arms were seen in myeloid-derived suppressor cells (MDSCs) post-therapy. Network medicine identified VEGF as target to reduce MDSCs. VEGF was found expressed by MDSCs of mainly responder patients. Differential gene expression analysis identified increased pro-inflammatory gene signatures in standard-dose arm. **Conclusions:** Overall PFS and OS were similar for nivolumab plus standard- or low-dose bevacizumab for rGBM, with post-hoc survival benefit seen in standard-dose arm in elderly. Standard-dose bevacizumab was associated with increased systemic inflammatory response and reduced immunosuppressive MDSCs. Clinical trial information: NCT03452579. Research Sponsor: None.

	N	ORR (%)	Progression Events	Median PFS(95%CI)	PFS-6 (95%CI)	Log-rank P-value
Standard-dose	42	15 (36%)	36 (86%)	141 (119-201)	37.9 (22.8,52.9)	0.83
Low-dose	45	17 (38%)	41 (91%)	139 (92-228)	42.9 (27.9,57.8)	

Small extracellular vesicles as a novel liquid biopsy approach for glioblastoma.

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Background: Glioblastoma (GBM) remains the most common and aggressive primary malignant brain tumor, and afflicted patients have limited options and poor overall survival. Diagnosis, prognosis, and assessment of treatment effectiveness is hampered by the absence of readily available sensitive, tumor specific, non-invasive blood-based assays which could be followed serially. Small extracellular vesicles (sEV) are nano-sized (≤200 nm) membrane bound bodies secreted by all cells, encapsulating cargo reflective of their parent cells. sEV have emerged as promising molecular indicator of a disease condition. Here, we report the feasibility of isolating glioma specific sEV (sEV^{glioma}) from the plasma and characterizing those for GBM specific molecular biomarkers. **Methods:** Plasma samples were collected from patients (n=31) diagnosed with adult gliomas (including grade 3 and 4 GBM, grade 2 and 3 astrocytoma) and healthy individuals (n=9). Total sEV (TE) population was isolated from plasma by a modified precipitation (ExoQuick) method. Next, sEV^{glioma} were isolated from the TE by an immunoprecipitation approach employing specific surface markers targeting cellular origin of gliomas, including astrocyte (GLAST and EAAT2), oligodendrocyte precursor cell (OSP and MOG), and neural stem cell (CD133). sEV^{glioma} were characterized for size and concentration by nanoparticle tracking analyses; surface expression of glioma specific biomarkers by nano-flow cytometry and confocal microscopy; and the expression of a panel of specific miRNAs by RT-PCR. Lastly, sEV^{glioma} were assessed by digital PCR for IDH1 status (wild type or mutated). **Results:** The average size of isolated sEV^{glioma} was less than 200nm. Importantly, compared to TE, sEV^{glioma} showed significant enrichment for glioma specific biomarkers such as ephrin type-A receptor 2 (14.7-fold), tenascin C (22.7-fold), and glial fibrillary acidic protein (8.4-fold) by nano-flow cytometry. Similarly, sEV^{glioma}, but not TE, demonstrated high expression of EGFRvIII (3.6-fold), a known biomarker for GBM. These results were confirmed by confocal microscopy. Interestingly, expression of specific miRNAs (miR-9a-5p, miR-16-5p, miR-21-5p) in sEV^{glioma} was higher in glioma patients with shorter survival (<12 months) compared to patients with longer survival (>20 months). Lastly, we successfully detected the existence of wild type IDH1 and absence of mutated IDH1 R132H in sEV^{glioma} from GBM patients. This approach was validated in sEV isolated from the conditioned media of IDH1-wild type GBM cell lines (A172 and T98G) and a IDH1-mutated cell line (BT54). **Conclusions:** We present a novel approach to isolate sEV^{glioma} from blood that could serve as a liquid biopsy, offering valuable molecular and genetic information. This approach promises early detection, potential to distinguish pseudo-progression, and assessment of treatment effectiveness with remarkable precision. Research Sponsor: None.

Intracranial hemorrhage in glioblastoma: Incidence, risk factors, and outcome.

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Background: The incidence and clinical implications of intracranial hemorrhage (ICH) in patients with glioblastoma have not been well studied. Risk factors for ICH and associations with therapy and outcome remain unknown. It has been speculated that prior radiotherapy, chemotherapy-associated thrombocytopenia, steroid medications as well as age, other comedications and comorbidities contribute to the risk of ICH in this patient population. **Methods:** We identified consecutive patients with glioblastoma per WHO 2021 definition from the electronic charts of the University Hospital in Zurich, Switzerland and explored the incidence, putative risk factors, management and outcome of ICH in patients with glioblastoma. ICH was identified on central MRI and imaging report review. The study has been approved by Swissethics (2023-00532). **Results:** Among 387 patients diagnosed between 2010 and 2019, 6 patients presented with ICH, and 22 patients experienced ICH in the further disease course, after a median time of 153 days (IQR 79-323 days). Of the 6 patients with ICH at diagnosis, 2 patients were on anti-platelet agents and 1 was on anticoagulation. ICH occurred in the tumor region in all these patients. There were no specific features in their history compared with patients that did not present with ICH at diagnosis. Among 22 patients with ICH after diagnosis, 9 patients (41%) experienced ICH prior to first progression. ICH were not restricted to the tumor region, but included subdural hematomas in 7 patients and an epidural hematoma in one patient. Fifteen patients (68%) were hospitalized for ICH, and 5 patients (23%) had a craniotomy. Thirteen patients (59%) had no change in management, 4 patients (18%) started a new intervention, and 5 patients (23%) went to palliative care. Compared with patients without any ICH ever documented, the 28 patients with ICH were more often male, but not older, did not have a history of arterial hypertension, diabetes, chronic kidney disease or smoking, and did not have larger tumors at diagnosis. At the timepoint of intracranial hemorrhage, six patients (27%) had been preexposed to bevacizumab, yet, 188 patients (53%) of the reference cohort received bevacizumab across the disease trajectory without experiencing an ICH. Three patients (14%) had platelet counts below 100,000/μl. Overall survival in the 28 patients who experienced an ICH was not inferior to survival in the population of patients without an ICH. **Conclusions:** ICH at diagnosis is rare in glioblastoma and its etiology remains to be identified. It may be related to intrinsic features of the tumor and its blood vessels since no other patient-related risk factors were identified. Overall, male sex was the only risk factor associated with ICH in this study, but ICH does not signify a poor outcome overall. Research Sponsor: None.

A phase II study of plerixafor combined with whole brain radiation therapy (WBRT) for patients with newly diagnosed glioblastoma.

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Background: Plerixafor inhibits the binding of stromal cell-derived factor 1 (SDF-1a / CXCL12) to its receptor on CD11b+ monocytes, inhibiting vasculogenesis and tumor recurrence in preclinical models. An early phase trial demonstrated that Plerixafor administration decreased cerebral blood volume (CBV) within the irradiated field of glioblastoma patients, and that the majority of recurrences occurred outside of the irradiated field (Thomas R. et al, Clin Cancer Res). This follow up study investigates the efficacy of Plerixafor in combination with WBRT, with the hypothesis that widening the radiation therapy (RT) field with WBRT may reduce out-of-field tumor recurrence and improve survival. **Methods:** This was a Phase II, open-label, non-randomized, single-arm trial.Adults between 18-75 years old with newly diagnosed high grade glioma as defined by WHO 2016 criteria and KPS $\geq$ 60 were eligible for enrollment. Patients underwent maximal safe resection followed by 6 weeks of concurrent radiation therapy and temozolomide (TMZ). Of note, modifications to the conventional treatment paradigm included completing 30 Gy of standard intensity-modulated RT followed by 30 Gy of WBRT, as well as completing a 4-week continuous infusion of Plerixafor dosed at 400 μg/kg/day. Patients then started adjuvant TMZ after completing Plerixafor. Primary endpoint was 6-month progression free survival (PFS6) after chemoradiation. Secondary endpoints included median overall survival (mOS), adverse events (AEs), MRI-based patterns of recurrence, and neurocognitive outcomes measured by the Trail Making Test, Controlled Oral Word Association Test, and the Hopkins Verbal Learning Test. Additionally, maximum arterial spin labeling-cerebral blood flow (ASL-CBF) values of primary lesions were compared over various time points during the study. **Results:** 14 of 17 enrolled patients completed the Plerixafor infusion, and all 17 patients completed WBRT. Median age was 57 years. 15 patients (88.2%) were IDH wildtype and 13 patients (76.5%) were pMGMT unmethylated. 13 patients (76.5%) underwent gross total resection, 2 (11.8%) underwent subtotal resection, and 2 (11.8%) underwent biopsy only. The PFS6 was 91.7%. The mOS was 15.11 months. 3 patients discontinued Plerixafor early due to rash (n=1), rising creatinine (n=1), or worsening confusion and agitation (n=1). Common Gr2 treatment-related AEs included alopecia (n=4), nausea (n=4), and vomiting (n=2). 1 patient had Gr3 alopecia. There were no Grade 4/5 AEs. 80% of patients scored worse on their neurocognitive assessments at 6 months compared to screening. ASL-CBF values of primary lesions appeared relatively stable throughout the study. **Conclusions:** The combination of Plerixafor and WBRT did not improve mOS compared to the original study using focused RT only. There was an overall decline in neurocognitive performance over the course of the study. Clinical trial information: NCT03746080. Research Sponsor: Sanofi-Aventis.

Phase I clinical trial of peposertib plus radiation in adults with newly diagnosed MGMT-unmethylated glioblastoma.

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Background: DNA-dependent protein kinase (DNA-PK) is a pivotal component of DNA damage repair (DDR) pathways and is an attractive target in glioblastoma because its expression renders tumors less vulnerable to radiotherapy. Peposertib is a small molecule DNA-PK inhibitor that has been pre-clinically shown to potentiate radiotherapy and regress glioblastoma tumors. We conducted a two-stage phase I trial of peposertib plus radiation in patients with newly-diagnosed MGMT-unmethylated glioblastoma (NCT04555577). **Methods:** In stage 1, patients received concurrent peposertib plus standard-of-care radiotherapy to determine the maximum-tolerated dose (MTD) based on the Bayesian Optimal Interval design (maximum n=24). Stage 2 is a window-of-opportunity expansion cohort and will include 5 surgical patients to evaluate intratumoral drug concentration. Both groups receive 6 cycles of adjuvant temozolomide. **Results:** Eighteen patients completed the 10-week dose-limiting toxicity (DLT) period; 3@50mg, 3@100mg, 3@200mg, 9@300mg. One DLT (G3 radiation necrosis [RN] at 300mg) was observed. Enrollment of the last three patients into the 300mg dose level began in December 2023 and will complete stage 1. To date, most notable toxicity was transient G3 dermatitis of the scalp (2@200mg, 1@300mg; not a DLT per protocol). Therefore, radiation dose constraints to the skin were incorporated and subsequent patients did not experience this toxicity. After a median follow up of 14.3 months (9.3-18.4), the median OS was 22.9 months [95% CI (16-NR)] and median PFS was 12.7 months [95% CI (9-NR)]. Next-generation sequencing (NGS) was available for 16 archival tumor tissue specimens from patients treated on this trial. Two patients had pathology-proven RN (one within and one outside of the DLT period). Both tumors had baseline mutations in DDR genes (i.e. *ATRX*, *DICER1*). Recurrent tissue was available for 4 patients after treatment with peposertib, 2 of which demonstrated gain of DDR gene mutations (2 *ATM* mutations in one patient and gain of *MAD2L2* mutation in another patient). **Conclusions:** The initial safety data of peposertib plus radiation in patients with newly-diagnosed MGMT unmethylated glioblastoma is favorable. The cases with RN in tumors with DDR mutations, the gain of DDR mutations in recurrent tumors, and the cases of scalp dermatitis suggest peposertib activity may correlate with DDR function, and possibly potentiates the effect of radiation. Stage I is an independent stage of the protocol that will enable MTD determination. Complete safety and survival data and correlations with genomics and spatial transcriptomics for Stage I patients will be presented at the meeting. The study was supported by EMD Serono (CrossRef Funder ID: 10.13039/100004755). Clinical trial information: NCT04555577. Research Sponsor: EMD-serono; CrossRef Funder ID: 10.13039/100004755.

A novel liquid biopsy assay with an 88% detection rate of genomic alterations across CNS tumors.

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Background: Diagnosis and treatment decisions for CNS tumors rely upon imaging with subsequent histological and genomic analyses of tissue to identify appropriate courses of therapy. Genomic profiling of tumor tissue for informative alterations is used to guide treatment, however contemporaneous tissue can sometimes be unavailable, inconclusive or overlook possible actionable alterations given the high amount of spatial heterogeneity in certain tumor types such as glioblastomas GBMs. Liquid biopsies may pose a possible solution, as they are readily accessible and provide a holistic snapshot of the tumoral genomic landscape. However, detection of ctDNAs from CNS tumors is impeded by its inherently low shedding biology and poor permeability across the BBB resulting in low plasma variant allele fractions (VAFs), with alteration detection rates ranging 27-55%. Thus, current assays do not yet have the sensitivity to be clinically useful in aiding decision making for CNS tumors. **Methods:** 62 cases of primary CNS tumors were submitted commercially for assessment with Northstar Select, a tumor-naive, plasma-based ctDNA liquid biopsy assay. Cases were obtained from a single clinic dating from January-December 2023. **Results:** See table. **Conclusions:** There remains an unmet clinical need for a highly sensitive liquid biopsy assay for use in determining the genomic landscape of CNS tumors to aid in clinical decision making. Current assays do not have a low enough limit of detection (LoD) to accurately detect ctDNAs at low VAFs. Herein, we demonstrate that Northstar Select has a detection rate of 88.7% in all cases and 91.4% in GBMs, nearly doubling current rates. This is due to the assay's uniquely low LoD of 0.13-0.16% VAF, which is below the 0.17% median VAF demonstrated across CNS tumors in this study, allowing for more low-abundance alterations to be detected. Given the increased total variant detection rate, nearly 50% of which were actionable when alterations were detected, these data support the clinical utility of Northstar Select to inform clinical decisions either as a complement to imaging and tissue analyses or independently when tissue biopsies are infeasible. These data further suggest that the clinical utility of Northstar Select may be expanded into metastatic brain disease and other low ctDNA shedding tumors. Research Sponsor: None.

	All CNS Cases	GBMs Only
Total cases	62	35
Cases w/ alterations	55 (88.7%)	32 (91.4%)
Cases w/ non-VUS alterations detected	25 (40.3%)	20 (57.1%)
Cases w/ VUS only detected	30 (48.4%)	12 (34.3%)
Cases with actionable alterations	22 (35.5%)	17 (48.6%)
Actionable alterations (therapy, trial or resistance marker)	43	33
Median VAF (25th-75th percentile)	0.17% (0.1-2.02%)	0.17% (0.11-1.5%)

VUS, Variants of unknown significance; VAF, variant allele fraction.

Pre-treatment immune biomarkers of pembrolizumab efficacy in patients with glioblastoma treated with standard of care.

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Background: Immune checkpoint inhibition with pembrolizumab has shown clinical benefits in multiple cancer types. However, success with checkpoint inhibition remains elusive in glioblastoma (GBM). Identifying patients *a priori* who would benefit from checkpoint inhibition with pembrolizumab in GBM may allow for improved survival. Currently there are no immune biomarkers that allow for selective treatment with pembrolizumab in GBM. **Methods:** The exploratory endpoint for our prospective single-arm study (NCT 03347617) evaluated longitudinal changes in immune cell sub-populations (B-cells, T-cells, NK cells, monocytes, and myeloid cells) in 50 newly diagnosed GBM patients who received standard of care chemoradiation with concurrent pembrolizumab after maximal safe resection. Flow cytometry was performed on blood collected at predetermined timepoints (pre-treatment, post-radiation, suspected progression, and confirmed progression) and immune cell sub-populations were evaluated as covariates in univariate and multivariate overall survival analysis while stratifying by IDH and MGMT methylation status and controlling for age and KPS using Cox proportional hazards regression in *R*. **Results:** Of the 56 patients enrolled in this trial, 50 were included in the analysis who had completed the pre-treatment blood collection. Median overall survival was 13.84 months. Nineteen patients (38%) were female and 31 (62%) were male. Median survival was 58 years (IQR: 46.25-69). Median KPS at study start was 90 (IQR: 80-90). MGMT methylation status included 23 (46%) patients not methylation and 25 (50%) hypermethylated patients, as well as 2 (4%) patients unidentified. IDH status included 39 (78%) wild-type patients, 10 (20%) mutant patients and 1 (2%) unidentified. At the pre-treatment timepoint, univariate analysis identified the following serum derived immune populations as being significantly associated with overall survival: cytotoxic T-cells (CD3+CD8+; HR: 0.98; p=0.094); CD4:CD8 ratio (HR:1.35; p=0.003); regulatory T-cells (4+127-BRIGHT25+; HR: 0.99; p=0.075); B-cells% (CD19+; HR:1.07; p=0.045). Multivariate analysis revealed significant association of CD4:CD8 ratio (HR:1.80; p=0.002) and regulatory T-cells (HR:0.98; p=0.015) with overall survival. **Conclusions:** GBM patients with increased serum CD4:CD8 ratios are associated with worsened overall survival prior to receiving standard of care chemoradiation and pembrolizumab. These results suggest that pembrolizumab should be withheld in patients with pre-treatment elevated levels of CD4:CD8 ratios. Alternatively, patients with higher serum regulatory T-cells have improved overall survival and may benefit from the addition of pembrolizumab. Validation of these results is needed in patients treated with standard of care versus standard of care plus pembrolizumab before implementing into clinical practice. Clinical trial information: NCT 03347617. Research Sponsor: None.

Phase 2 study of bizaxofusp, an IL-4R targeted toxin payload, in nonresectable recurrent GBM: Comparison of overall survival with contemporaneous eligibility-matched and propensity score balanced external control arm.

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Background: Bizaxofusp (MDNA55) is designed to selectively deliver a potent toxin payload to tumor cells by targeting the IL-4 receptor (IL-4R) overexpressed by GBM, but not normal brain. Localized delivery of bizaxofusp minimizes risk of off-target toxicities and systemic exposure while eliciting effective tumor cell killing. Bizaxofusp was evaluated using convection-enhanced delivery in MDNA55-05 (NCT02858895), a single-arm, open-label, multi-center Ph2 study in nonresectable recurrent GBM (rGBM). **Methods:** The study population comprised of de novo IDH wild-type GBM patients with 1st or 2nd relapse that were non-resectable. Forty-four patients were administered a single treatment of bizaxofusp (range: 18-240 μg). The primary endpoint was OS; secondary endpoints were safety and tumor response. IL-4R expression in tumor biopsies was determined using a validated assay. OS was compared to an eligibility matched external control arm (emECA) of 81 contemporaneous rGBM subjects receiving standard of care. The emECA was further refined by propensity-score balancing (pbECA) to the bizaxofusp arm based on known prognostic factors, resulting in a weighted sample size of 40.8. OS was defined as time from relapse (to unify index date in both arms) or treatment start (for analysis of tumor response) to death/censor. Tumor response was assessed following RANO and mRANO criteria. **Results:** Bizaxofusp showed an acceptable safety profile at doses up to 240 μg. TRAEs were primarily neurological or aggravation of pre-existing neurological deficits associated with GBM and were manageable with standard measures. Results showed that IL-4R expression did not impact mOS except in patients receiving low doses of bizaxofusp. The bizaxofusp arm had significantly longer median OS (mOS) than contemporaneous emECA (12.4 vs 7.7 months; HR: 0.64, 95% CI 0.46-0.93; p = 0.02). Survival benefit was also evident when compared to the pbECA: (12.4 vs 7.2 months; HR: 0.72, 95% CI 0.46-1.1; p = 0.27). Patients with tumor control (SD or PR/CR, n=21) had significantly longer mOS than patients with tumor progression (n=23) (16.7 vs 8.5 months; HR = 0.5, 95% CI 0.27-0.9; p = 0.01). Among patients with tumor control who had pseudoprogression (PsP) per mRANO, mOS (22.8 months) was significantly longer than patients with tumor progression (HR: 0.49, 95% CI 0.25-0.98; p = 0.049). **Conclusions:** Bizaxofusp achieved significant OS benefit in patients with nonresectable rGBM compared to contemporaneous emECA. Patients who experienced tumor control, including those with PsP, showed significantly longer survival than patients with tumor progression. Phase 3 ready registrational trial will comprise a high dose bizaxofusp arm and a hybrid control arm with 1/3 randomized subjects and 2/3 pmECA. Clinical trial information: NCT02858895. Research Sponsor: Cancer Prevention and Research Institute of Texax.

Therapeutic insights for the aggressive subset of high-grade gliomas (HGG) driven by chromosome 1q32 *MDM4-containing* amplicon and unmethylated *MGMT*.

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Background: *MDM4/MDMX* amplification (*MDM4* amp) is associated with poor outcomes, including after immune checkpoint blockade therapy, in multiple tumor types (El-Deiry et al., ASCO, 2022). Glioblastoma (GBM) displays the highest rate of *MDM4* amp (9.63%) among all tumor types (Arnoff and El-Deiry, 2022). *MDM4* located on chromosome 1q32 can be amplified separately from contactin 2 (*CNTN2*) although they can be co-amplified among 17 genes with *MDM4* as main amplification target (Riemenschneider et al., 2003). There are no FDA-approved drugs targeting MDMX although there are preclinical compounds such as XI-006 (NSC208895) that can reduce cell migration (George et al., AACR, 2023; De La Cruz, AACR, 2023). We recently uncovered immune-stimulatory effects of temozolomide (TMZ) within hours of drug exposure, prior to cell division and mutation accumulation in microsatellite stable colorectal cancer and HGG (Gonzalez et al., 2023). Here we explored *MDM4* amp, co-expressed genes, *MGMT*, clinical outcomes and response to TMZ. **Methods:** HGG tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA and RNA (NGS) were analyzed. *MDM4* amp was determined with a cutoff of >/= 4.0 copies. MGMT promoter methylation (me) was tested by pyrosequencing. Patient outcome was obtained from insurance claims data and calculated from start of TMZ (tmzOS) or tissue collection to last contact (rwOS). Cox proportional hazards model, X^2/Fisher-Exact was used and p values were adjusted for multiple correction (q value) when appropriate. **Results:** In a large cohort of 3856 HGG wild-type for IDH1/2, H3F3A and TP53, 300 (8.4%) had MDM4 amp and showed a shorter OS compared to MDM4-not amplified tumors (median rwOS: 14.9 vs 17.3 mo, HR: 1.286; 95% CI: 1.12-1.48, $p<0.001$). The effect is significant after accounting for age and gender (adjusted p=0.016). *MDM4* amp was associated with increased PIK3C2B (fold change: 6.7) and PPP1R15B (FC: 7.9, both $q<0.01$) expression among other candidates for co-targeting present on Chr 1q32.1; while no significant difference was seen with MGMT-me (p=0.3). Among patients with unmethylated MGMT treated with TMZ (N=1066), MDM4 amp (N=101) was associated with shorter tmzOS (14.3m vs. 15.9m, HR: 1.27, 1.01-1.59, p=0.038) while a trend was seen in the 926 methylated patients (MDM4 Amp: 69, not amplified: 857; tmzOS: 22 m vs. 27.7m, HR: 1.33; 0.95-1.85), p=0.092.). **Conclusions:** *MDM4* amp is negatively associated with clinical outcomes in TP53-WT HGG. The *MDM4*amplicon on Chr 1q32.1 has associated targets such as PIK3C2B and phosphatase PPP1R15B that may be suitable for therapeutic targeting in a subset of aggressive HGG's with *MDM4* amp. The Chr 1q32 amplicon contains therapeutic targets known to attenuate immune responses and thus their targeting may be combined with various treatments including immunotherapy, targeted therapies, chemotherapy or vaccines. Research Sponsor: None.

Racial/ethnic disparities in healthcare utilization, post-operative outcomes, and overall survival for IDH-wildtype glioblastoma stratifying by *MGMT* promoter methylation status.

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Background: Glioblastoma is the most common malignant primary brain tumor and molecular profiles such as *IDH*1/2 and *MGMT* promoter methylation status have significant influence on survival outcomes. There is no "real-world" study has investigated the racial/ethnic disparities in healthcare utilization and outcomes for *IDH-wildtype glioblastoma patients with MGMT* promoter methylation status. **Methods:** A total of 21971 *IDH*-wildtype glioblastoma patients (*MGMT* promoter-methylated: 41.5%, 9110/21971) were derived from the National Cancer Database (NCDB, 2018-2021). Race/Ethnicity was grouped into Non-Hispanic White (NHW), Non-Hispanic Black (NHB), Asian/Pacific Islander (API), American Indian/Alaska Native (AIAN), Hispanic, and Others. Overall survival (OS) was set as primary outcome. Healthcare utilization and post-operative outcomes are secondary endpoints. Multivariable logistic regression models, Kaplan-Meier methods, and Cox proportional hazards models were performed for post-operative outcomes, healthcare utilization, and overall survival. **Results:** Compared to NHW, AIAN were 78% more likely to have *MGMT* promoter methylation after adjusting age and gender (aOR=1.78, p=0.030). API and Hispanic were significantly less likely to undergo GTR over STR comparing to NHW. The odds of receiving chemotherapy and RT for race/ethnicity minorities patients were significantly lower than NHW (Chemotherapy: NHB: aOR=0.79, AIAN: aOR=0.57, Hispanic: aOR=0.83; RT: NHB: aOR=0.88, Hispanic: aOR=0.80). The median OSs by race/ethnicity (NHW, NHB, API, AIAN, Hispanic, and Others, respectively) were: 11.5, 12.3, 14.5, 9.2, 13.6, and 15.6, months (*MGMT* promoter-unmethylated, $p<0.001$), 15.9, 18.8, 23.7, 14.8, 19.6, and 15.5, months (*MGMT* promoter-methylated, $p<0.001$). After adjusting the covariates, NHB, API, and Hispanic experienced significantly lower risk of death comparing to NHW (aHR=0.82, 0.66, and 0.75, all $p<0.001$). Similar results were validated in stratification analysis by *MGMT* promoter methylation status, except MGMT promoter-unmethylated AIAN experienced 70% higher risk of death than NHW (aHR=1.70, p=0.021). **Conclusions:** Our findings suggests that racial/ethnic disparities exist in healthcare utilization, postoperative outcomes, and overall survival in *IDH*-wildtype glioblastoma population. Research Sponsor: None.

Unraveling the immunologic vulnerabilities of diffuse hemispheric glioma, H3 G34-mutant.

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Background: Recent insights into the molecular basis of diffuse hemispheric glioma, H3 G34-mutant (DHG-G34), an incurable high-grade glioma, have opened new therapeutic possibilities. The oncohistone mutation in DHG-G34 impairs the epigenetic regulator SETD2, which normally orchestrates DNA-mismatch-repair and negatively regulates the transcriptional silencing activity of the Polycomb Repressive Complex 2 (PRC2). In DHG-G34, a mismatch-repair-deficiency phenotype is predicted, but an anti-tumor immune response is notably absent in clinical observations, which we posit is linked to the aberrant transcriptional repression by PRC2. Here, we investigate DHG-G34 immunosuppression mechanisms in a large real-world multi-omics cohort and human cell lines. **Methods:** Clinical, molecular, and immunologic characteristics of a DHG-G34 cohort, sequenced (DNA and RNA) at Caris Life Sciences (Phoenix, AZ), are contrasted against diffuse midline glioma (DMG) and pediatric low-grade glioma (LGG). A significant difference between genomic subgroups was defined as fold-change > 1.2. Statistical significance was determined using chi-square, Fishers-exact, and Mann Whitney U tests with corrections for multiple hypothesis testing ($q < 0.05$).Hazard ratio (HR) was calculated using the Cox proportional hazards model. KNS-42 DHG-G34 cell line was exposed in triplicate to 1 μM valemetostat (an EZH1/2 inhibitor) or DMSO in vitro. Flow cytometry and RNA-sequencing were utilized to determine differential immunologic characteristics. **Results:** 29 DHG-G34, 51 DMG, and 52 LGG were identified in Caris database. Median OS among DHG-G34 was 15.4 mo., similar to DMG (HR = 1.1, 95% CI: 0.70-1.73, p = 0.686). Most frequent alterations in DHG-G34 were *TP53* (93.1%), *ATRX* (69.0%), *PDGFRA* (31.0%). Tumor mutational burden (TMB) was high, >=10mt/MB, in 10% of DHG-G34 and 0/51 in DMG and 0/52 LGG ($p < 0.01$, $q > 0.05$), but immune fractions including dendritic cells, T cells, macrophages, microglia, and antigen-presenting genes were decreased (fold-change: 0.19 – 0.83, $q < 0.05$). In KNS-42, PRC2 inhibition upregulated MHC class 1 ($p < 0.001$). Of 402 KNS-42 missense variants, transcription of 43 were upregulated following EHZ2 inhibition, and 4 were downregulated ($q < 0.05$). Among immunostimulatory genes, *P2RX7*, which engages T-cells and stimulates an inflammatory response, was downregulated in patient samples ($q < 0.001$) and upregulated in KNS-42 following EZH2 inhibition ($q < 0.001$). **Conclusions:** DHG-G34 has an increased propensity for high TMB but remains immunologically cold. Our pilot experiment suggests inhibiting PRC2's unique role in DHG-G34 may sensitize DHG-G34 to an immune response by inducing MHC class 1 expression and transcriptional readthrough of mutated transcripts. Understanding whether treatment induces TMB in DHG-G34 may affect timing of an immunotherapeutic intervention. Research Sponsor: None.

NFKBIA deletions reshape the epigenome antithetical to the *IDH* mutation and indication of prognosis in diffuse gliomas.

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Background: Genetic alterations help predict the clinical behavior of diffuse gliomas, but some variability remains uncorrelated. The *NFKBIA* gene at 14q13.2 encodes IkBa, a protein that regulates the activity of NF-kB in the cytoplasm. Evidence that, in chromatin, nuclear NFKBIA dynamically interacts with histones H2A and H4 to regulate polycomb-dependent transcriptional repression and, thus, stem cell maturation and lineage specification and our characterization of *NFKBIA* as a tumor suppressor in glioblastoma prompted our investigation of the relationship of *NFKBIA* deletions to other genetic markers, alterations in the methylome, and the clinical course of gliomas. **Methods:** We analyzed the genetic profiles of 2,343 WHO grade 2 to 4 diffuse gliomas in multiple clinically well-characterized patient populations, including national randomized phase III consortium trial RTOG 9802, to determine whether incorporation of *NFKBIA* deletions could enhance the prognostic value of current molecular descriptions. **Results:** We demonstrate that haploinsufficient deletions of *NFKBIA* display distinct patterns of occurrence in relation to other genetic markers, including driver mutations *IDH*, *TERT*, *ATRX*, and *PTEN*, 1p19q codeletion, and *CDKN2A/B* deletion, and are disproportionally present at recurrence. *NFKBIA* haploinsufficiency is associated with unfavorable patient outcomes, independent of genetic and clinicopathologic predictors. *NFKBIA* deletions reshape the DNA and histone methylome antipodal to the *IDH* mutation. The methylome changes facilitated through *NFKBIA* deletions engender a transcriptome landscape partly reminiscent of *H3K27M* mutant pediatric gliomas and are highly enriched for neural stem cell and neurogenesis genes bearing repressive H3K27 marks. Our findings imply that the *NFKBIA* deletion in adult gliomas and the *H3K27M* mutation in pediatric diffuse midline gliomas define aggressive disease subtypes that may share an epigenetic state reflecting a common PRC2 loss-of-function phenotype antipodal to the quasi PRC2 gain-of-function phenotype of *IDH* mutant gliomas and their favorable clinical course. Lower-grade gliomas harboring *NFKBIA* deletions behave much like high-grade gliomas. In *IDH* mutant gliomas, *NFKBIA* deletions are common in tumors with a clinical course similar to that of *IDH* wildtype tumors. A sparse, easily interpretable, and externally validated nomogram model for estimating individual patient survival in *IDH* mutant gliomas, incorporating *NFKBIA* deletion and current best-established genetic and clinicopathologic factors, confirms that *NFKBIA* deletions predict comparatively brief survival. **Conclusions:** *NFKBIA* haploinsufficiency aligns with distinct epigenome changes, portends a poor prognosis, and should be incorporated into clinical models predicting the disease fate of diffuse gliomas. Research Sponsor: National Cancer Institute; UG1CA189867; U10CA180822.

Global, national, and regional burden of brain and central nervous system cancer in youth under 20 from 1990-2019: A benchmarking analysis.

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Background: Brain and central nervous system (CNS) cancer ranks as the second leading cause of death among all cancer-related fatalities globally in individuals under 20 years old. Despite its significance, there is a notable dearth of data on brain and CNS cancer in this age group, necessitating a comprehensive cross-country comparison. **Methods:** Utilizing the Global Burden of Disease study framework, we estimated the prevalence, incidence, deaths, and disability-adjusted life years (DALYs) attributable to brain and CNS cancer by age, sex, year, and location across 204 countries and territories from 1990-2019. **Results:** The total prevalence increased from 153,334 (95%UI: 111,452-233,819) in 1990 to 212,459 (164,908-245,556) in 2019, with incidence rising from 47,373 (32,635-74,710) in 1990 to 47,600 (36,572-55,194) in 2019. Notably, the annual percentage change (APC) in deaths decreased by 21% (56-15), and DALYs by 22% (57-15) from 1990-2019. Sub-Saharan Africa and the African Union exhibited the highest APC increase in deaths, while Southeast Asia, East Asia, and Oceania experienced the most significant decrease. The highest APC in incidence occurred in the 10-14 years age group at 27%, with a slight increase of 1% in deaths observed in the 10-19 years age group. Females bore a higher burden compared to males, with APC in prevalence at 29% versus 51%, and incidence at -4% versus 7%. **Conclusions:** Brain and CNS cancer accounted for 9.55% of deaths among individuals under 20 globally in 2019. While the overall global trend has shown an increase over the last three decades, females exhibit a higher burden. Despite a decrease in deaths over the same period, strategies must be implemented to combat this burden, emphasizing the importance of early investigation and management, particularly in resource-limited settings worldwide. Research Sponsor: None.

	Incidence			Deaths			DALYs		
Region	1990	2019	APC (%)	1990	2019	APC (%)	1990	2019	APC (%)
Western Pacific Region	15981	11928	-25	10200	4403	-57	838182	359671	-57
South-East Asia Region	11020	9439	-14	7764	5849	-25	646927	477367	-26
Region of the Americas	5552	6565	18	2923	2977	2	238648	240784	1
European Region	6814	5645	-17	3766	2288	-39	305599	184916	-39
Eastern Mediterranean Region	4639	7769	67	2783	3858	39	231085	316136	37
African Region	3264	6101	87	2240	4097	83	187899	339000	80

APC: Annual percentage of change, DALYs: disability adjusted life years.

2085 Poster Session

A 16 year-retrospective study of refractory meningiomas: Prognostic factors and systemic treatments.

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Background: Meningiomas are the most common brain tumors, with no established standard systemic treatment for refractory cases after surgical and radiotherapeutic interventions. This study aims to identify prognostic factors for overall survival in refractory meningioma and document patient evolution with systemic treatments. **Methods:** In a retrospective study, we identified patients with meningioma initially followed at CHUM university hospital between 2006 and 2022. Patients with progression after first-line treatment and over 6 months of follow-up were included. The population was divided into two: group 1 received surgery and/or radiotherapy for progression, and group 2 received additional systemic treatments. Survival analysis with Kaplan-Meier curves and group comparisons (Log-Rank, Fisher's Exact Tests) were conducted. **Results:** A total of750 patients with meningioma were identified. 99 (13%) progressed after first-line treatment. Among them, 70 (9%) were categorized in group 1 and 29 (4%), in group 2. The median follow-up time from diagnosis was 7.5 years. The overall 10-year survival rate was higher in group 1 compared to group 2 (88% vs 62%). Prognostic factors affecting survival were identified as the following: disease progression after second-line treatment, age $\geq$ 65 years, and grade 2 or 3. When comparing PFS-1 after first-line treatment, they were similar between group 1 and group 2 (mPFS-1: 2.63 vs 3.49 years; p = 0.421). However, PFS-2 after second-line treatment was significantly shorter in group 2 (mPFS-2 : 12.6 vs 2.3 years ; $p < 0.001$). Age of $\geq$ 65 years (10-year survival: 57% vs 89%; $p < 0.001$) and higher grades (10 year survival: 90% grade 1 vs 58% - grade 2 vs 75% - grade 3; p = 0.027) were associated with lower survival rates. The number of lesions (unique or multiple) and localization (supra or infratentorial) of tumors had no significant impact on survival (p=0.257; p = 0.482). Regarding systemic treatments, 7 patients (25%) received Bevacizumab. It was the treatment associated with the longest PFS (mPFS = 22.5 months) when compared to Hydroxyurea (n=18 [62%], mPFS = 4 months), Somatostatin (n = 5 [17%], mPFS = 8 months), a combination of Hydroxyurea and Somatostatin (n=7 [24%], mPFS = 8 months) and Sunitinib (n=3 [10%], mPFS = 14 months). For patients discontinuing systemic treatment, median survival was 5 months. Systemic treatments were well-tolerated. Among moderate to severe side effects (grade $\geq$ 2), we documented bradycardia (Somatostatin, n=1), elevated liver enzymes (Sunitinib, n=1), anemia and neutropenia (Hydroxyurea, n=3) and proteinuria (Bevacizumab, n=1). **Conclusions:** Prognostic factors for survival in meningioma include age $\geq$ 65 years, grades 2 and 3, and the occurrence of a second progression. Our study highlights Bevacizumab in systemic treatment strategies which was well tolerated in our patients. Research Sponsor: None.

Real-world monitoring and treatment patterns in von Hippel-Lindau (VHL) disease-associated central nervous system hemangioblastomas (CNS-Hb).

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Background: VHL disease is an inherited tumor syndrome that causes multiple benign and malignant tumors to develop; CNS-Hb is often the first VHL disease manifestation, occurring in 70-80% of patients with VHL. Patients often need many tumor treatments to manage the disease. This study evaluated disease monitoring and treatment patterns among patients with VHL-CNS-Hb. **Methods:** Using an algorithm based on VHL manifestations, patients with VHL were identified from Optum's de-identified Clinformatics Data Mart Database. Patients with a CNS-Hb diagnosis were then selected. Treatment patterns were assessed among patients with VHL after their initial diagnosis of CNS-Hb. Incidence rates (IR) of the following treatments for managing CNS-Hb or other VHL-associated tumors were assessed: surgery for removal of VHL-associated tumors, renal ablation, radiotherapy, targeted therapy for RCC, and retinal laser therapy. Rates for tumor treatments were reported as events per 10-person years. Generalized linear models estimated IRs of analgesic use, VHL disease monitoring procedures, and visits to VHL-related medical specialists in the patient and control cohorts, adjusting for age, sex, the number of outpatient visits at baseline, and health plan type. **Results:** 220 patients with VHL-CNS-Hb were identified. Reflecting the multifaceted nature of VHL disease, the tumor treatments with the highest unadjusted IRs during the study period among these patients were targeted RCC therapies (2.15 per 10-person years), surgical removal of cerebellar and spinal hemangioblastomas (0.52 per 10-person years), and radiotherapy (0.42 per 10-person years). The tablecontains estimated adjusted IRs and IRRs for the use of select analgesics, monitoring procedures, and medical specialist visits for the VHL-CNS-Hb and comparator cohorts. **Conclusions:** VHL-CNS-Hb presents a multifaceted burden, involving treatments for various VHL-related tumors. Patients with VHL-CNS-Hb use more analgesics, undergo frequent monitoring, and have increased specialist visits compared with the control group. Successful tumor control holds the potential to reduce morbidity and long-term medical management associated with the disease. Research Sponsor: Merck & Co.

Analgesic use, monitoring procedures, and medical specialist visits.

	Adjusted IR VHL-CNS-Hb Cohort [per-person year]	Adjusted IR Control Cohort [per-person year]	aIRR (95% CI)	P-value
Any analgesic use	5.28	2.70	1.96 (1.45, 2.64)	< 0.001
Opioids	2.35	1.00	2.35 (1.54, 3.58)	< 0.001
Any monitoring procedure	7.80	1.99	3.93 (3.15, 4.90)	< 0.001
Renal function tests	2.38	1.00	2.39 (1.98, 2.88)	< 0.001
CT scans	1.81	0.23	7.81 (5.41, 11.28)	< 0.001
MRI imaging	0.85	0.11	8.07 (6.30, 10.34)	<0.001
Medical specialist visits				
Oncology	1.03	0.14	7.47 (4.19, 13.29)	< 0.001
Nephrology	0.72	0.04	20.30 (6.37, 64.68)	< 0.001
Neurosurgery	0.66	0.03	25.44 (14.34, 45.14)	<0.001

Emavusertib (CA-4948) in combination with ibrutinib in patients with relapsed/refractory primary central nervous system lymphoma (R/R PCNSL).

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Background: PCNSL is a rare and aggressive form of NHL in the central nervous system or vitreoretinal space. Despite high initial rates of responses to HD-MTX-based induction chemotherapies, most patients relapse in two years. R/R PCNSL is associated with poor prognosis, representing a clear unmet medical need, as there are no currently approved treatments for this disease. IRAK4 kinase activity is required for TLR and IL-1R signaling in a variety of myeloid and lymphoid cell types, including PCNSL. Recruitment of IRAK4 to these receptors and subsequent activation is facilitated by the MyD88 adaptor protein, which is mutated in ~70% of PCNSL. This leads to constitutive activation of the NF-κB signaling pathway, increased inflammation, and tumor growth. Emavusertib is a novel and potent oral inhibitor of IRAK4 and FLT3, which has demonstrated the ability to cross the blood-brain barrier in PCNSL xenografts. In preclinical studies, the combination of emavusertib with ibrutinib overcomes resistance to BTK inhibitors. This combination has an acceptable safety profile across a broad population of R/R NHL patients, including PCNSL. Here we present updated safety and efficacy data for emavusertib in combination with ibrutinib in patients with R/R PCNSL. **Methods:** The safety, clinical activity, and potential biomarkers of emavusertib in R/R PCNSL are being investigated in the ongoing open-label, Phase 1/2 TakeAim Lymphoma trial (NCT03328078). The eligible patients with R/R PCNSL received emavusertib (100-300 mg BID) in combination with ibrutinib (560 mg QD) in a 21-day cycle until tumor progression or unacceptable toxicity. **Results:** Here, we present updated data from R/R PCNSL patients with prior ibrutinib exposure who were treated with emavusertib in combination with ibrutinib. The median number of prior lines of anti-cancer therapies was 3 (range: 2-5), all patients were R/R to both frontline therapy and subsequent ibrutinib regimens. Prior responses to ibrutinib based regimens included only 1 CR. Here, we report a higher CR rate when these patients are subsequently treated with emavusertib in combination with ibrutinib.Results revealed no dose-limiting toxicities. **Conclusions:** Emavusertib in combination with ibrutinib was well tolerated with an acceptable safety profile and promising efficacy in R/R PCNSL patients with previous exposure to ibrutinib (BTKi). Enrollment in this trial is ongoing (NCT03328078). Clinical trial information: NCT03328078. Research Sponsor: Curis.

Marrow-ablative consolidation chemotherapy (HDCT) to decrease the development of choroid plexus carcinoma (CPC) specific relapse in high-risk TP53-mutated (germline or somatic) young children with newly diagnosed CPC.

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Background: Choroid plexus carcinomas (CPC) are highly malignant, early childhood cancers in which the loss of TP53 function is a central element of their development and defines unfavorable disease. To date, CPC-free survival rates have remained poor; recent data from St. Jude including complete TP53 mutation status, yielded CPC-free survival of only 29% with a non-marrow-ablative chemotherapy strategy. The rarity of CPC has constrained the ability to explore the role of HDCT with autologous hematopoietic progenitor cell rescue (AuHPCR). Previously reported results of the "Head Start" (HS) HDCT approach showed some promise of cure, but were limited by small patient numbers, short follow-up and incomplete TP53 mutation data. Consequently, the role of HDCT and AuHPCR in TP53-mutated CPC remains unclear. **Methods:** We have analyzed data on TP53 status, therapy, treatment responses, CPC-free and overall survivals (OS) and second cancers from the largest cohort of such patients, all who received initial therapy with the intent/consideration of undergoing consolidative HDCT. **Results:** Twenty-seven children with CPC (median age, 16 months) received HS-like induction chemotherapy regimens or ICE with the intent of utilizing consolidative HDCT. Twenty-three of 27 completed HDCT consolidation; the remaining 4 patients did not proceed with HDCT due to parental choice. Somatic or germline TP53 mutations were identified in 17 patients, while 4 patients exhibited TP53 wild type (TP53wt); TP53 status remains untested or unavailable in 6 patients. Five-year CPC-free survival and OS for the entire cohort were 47.8% and 44.4%. CPC-free survival for those with TP53 germline mutations (n=12) was 66%, for those with somatic tumor TP53 mutations (n=5) was 40% and for those with confirmed TP53wt (n=4) was 50%. The 5-year CPC-free survival for all 23 patients who underwent HDCT and AuHPCR was 52%, comprising 3/4 TP53wt patients, 10/12 TP53 germline mutated patients and all 5 TP53 somatic tumor mutated patients. Notably, all six survivors with TP53 mutations had undergone HDCT with AuHPCR, and all but one avoided irradiation. Eight out of 12 patients with documented genotypic (TP53 germline mutated) Li-Fraumeni Cancer Predisposition Syndrome (LFS) developed second malignancies. **Conclusions:** Our data indicate that HDCT with AuHPCR consolidation is associated with improved CPC-free survival compared with historical reports in young children with high-risk TP53 mutated CPC. However, the ultimate development of second cancers substantially affects outcomes for those with LFS, irrespective of HDCT treatment. These data justify the inclusion of HDCT and AuHPCR in the prospective international trial under development for young children with newly diagnosed TP53 mutated CPC.
Research Sponsor: None.

TPS2089 **Poster Session**

A multicenter phase 1 trial of tucatinib, trastuzumab, and capecitabine with stereotactic radiosurgery in patients with brain metastases from HER-2–positive breast cancer (TUTOR).

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Background: 20-40% of HER-2-positive breast cancer patients develop brain metastases (BMs), for which stereotactic radiosurgery (SRS) is used for local disease control. Tucatinib, an oral HER-2-selective tyrosine kinase inhibitor (TKI), has been demonstrated to be safe and efficacious in HER-2-positive breast cancer in combination with capecitabine and trastuzumab. The synergism between these three drugs and radiation may potentially enhance DNA damage, causing increased apoptosis. We hypothesize that this 3-drug therapy, in combination with SRS in patients with HER-2 positive breast cancer BM (BCBM), may be safe and provide superior long-term control of intracranial and systemic disease. **Methods:** This is a prospective, single-arm, multicenter, ongoing, phase 1 clinical trial. Patients aged 18-80 years, ECOG score 0-2, normal organ function, and up to 10 newly-diagnosed BMs is planned to enroll at six centers in the US. Any number of prior systemic therapies are allowed, except tucatinib and capecitabine. Key exclusion criteria include leptomeningeal metastases, evidence of intratumoral or peri-tumoral hemorrhage, and BMs within 5 mm of the optic chiasm/nerve. Patients receive oral tucatinib alongside SRS, followed by a two-week dose-limiting toxicity (DLT) period, and subsequently continue the regimen until disease progression or intolerable toxicity. DLTs are defined by Grade 3 or 4 thrombocytopenia, grade 4 anemia, grade 4 neutropenia lasting more than seven days, febrile neutropenia, and grade 3 non-hematologic toxicity. Primary study endpoint is maximum tolerated dose (MTD) of tucatinib in combinatorial therapy. This de-escalation study starts at 300 mg dose level (DL), with DL-1 250 mg, and DL-2 200 mg, based on a 3 + 3 design. Cohort expansion at MTD is planned to a total of 40 patients. Secondary endpoints include efficacy as determined by response rate, intracranial progression-free survival (PFS), extracranial PFS, overall survival, quality of life as assessed by FACT-Br, toxicity, and neurocognitive function. The trial has been approved by the Institutional Review Board (IRB) and currently is enrolling patients. Clinical trial information: NCT05553522. Research Sponsor: None.

TPS2090 Poster Session

A first-in-human phase 1 trial of dose escalating intrathecal (IT) dendritic cells (cDC1s) primed against HER2/HER3 in patients (pts) with leptomeningeal disease (LMD) from triple-negative (TNBC) or HER2+ breast cancer (BC).

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Background: Leptomeningeal disease (LMD) is a devastating complication of BC where it occurs in approximately 5% of pts and has a dismal prognosis. The CSF of pts with LMD have an innate (PMID:34035069), but not adaptive, immune response (bioRxiv 2023.03.17.533041; doi: https://doi.org/10.1101/2023.03.17.533041) that is insufficient to combat LMD. We used IT cDC1 to elicit an adaptive response in murine LMD and found that IT cDC1s were safe, induced a Th1 response, cured most HER2+ LMD, and prevented LMD recurrence (PMCID: 9354231). This Th1 response was CD4+ > CD8+ T cell dependent and produced marked B cell infiltration in the CSF. Mechanistic studies are in progress. These cDC1s have been shown to induce Th1 responses to HER2 and HER3 tumors and prolong survival in preclinical models (PMID: 35710296; PMID: 34785506). And there are several trials of cDC1s in BC patients that are ongoing (NCT03384914, NCT03387553, NCT05504707, NCT05325632, NCT04348747, NCT05378464). On the basis of our murine studies we hypothesized testing cDC1 therapy in pts that a RP2D would be found and the CSF following cDC1 therapy would be remodeled to have a Th1 adaptive immunological profile. **Methods:** This is a phase I single-arm, non-randomized dose escalation multicenter study to establish 1) the safety of IT cDC1s in pts with LMD, and 2) associations between clinical outcomes & translational CSF studies such as scRNAseq and cytokine/chemokine arrays. Eligibility includes TNBC or HER+ LMD pts, prior pCSpRT/WBRT, ECOG PS ≤2, cytologic or MRI diagnosis of LMD, normal marrow and organ function, life expectancy of ≥ 8 weeks, and an Ommaya reservoir in place. Exclusions included other treatments to treat LMD ≤ 2 wks or < five $^1/_2$ lives, > 8mg of DXM/D or equivalent, pregnancy or immunodeficiency syndromes were excluded. IT cDC1s were administered once a week x 12 wks at one of 4 dose levels ($1 \times 10^6 - 5 \times 10^7$ cDC1s) until PD, DLT or withdrawal during those 12 wks. Primary Endpoints was to 1) determine the safety and DLTs, and 2) association between various clinical endpoints and immune profiles in the CSF. We used the Bayesian Optimal Interval (BOIN) design to find the MTD. Response was measured using RANO-LM (PMID: 30715514). DLTs were defined as ≥ gr. 3 not due to LMD & didn't respond to medical intervention/CSF removal ≤ 96 hrs. Final pre & post cDC1 treatment cyto-, chemokine profiles and cellular/tumor profiles (scRNAseq) will be determined and associations between these and clinical endpoints will be determined. As of 01 30 2024 the 1st cohort closed with three pts (1 TNBC, 2 HER2+ pts)at the dose of 1×10^6 cDC1s. Clinical trial information: NCT05809752. Research Sponsor: U.S. Department of Defense.

TPS2091 **Poster Session**

Patritumab deruxtecan (HER3-DXd) in active brain metastases from metastatic breast and non-small cell lung cancers, and leptomeningeal disease from advanced solid tumors: The TUXEDO-3 phase II trial.

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Background: Brain metastases (BM) are a common and severe complication of cancer, resulting in increased morbidity and mortality. Highest incidence of BM is observed in advanced non–small cell lung cancer (aNSCLC) and metastatic breast cancer (mBC). Metastatic solid tumors with leptomeningeal disease (LMD) have a dismal outcome. Patients (pts) with BM and/or LMD have very limited treatment options. Antibody drug conjugates have shown high intracranial response rates and HER3 is highly expressed in CNS metastases of aNSCLC and mBC. Patritumab deruxtecan (HER3-DXd), an antibody drug conjugate combining an anti-HER3 antibody with a topoisomerase I inhibitor. It has demonstrated promising results in mBC and EGFR-mutated NSCLC, as shown in the HERTHENA-Lung 01 study, in which a CNS objective response rate (ORR) of 33.3% was achieved. We hypothesized that HER3-DXd may have clinical activity in active BM from mBC and aNSCLC, and in LMD from metastatic solid tumors. This study aims to evaluate the efficacy and safety of HER3-DXd in these pts. **Methods:** This is an international, multicenter, single-arm, three-cohort, phase II trial (NCT05865990). A total of 60 evaluable pts (20 per cohort) will be recruited from Austrian and Spanish hospitals and assigned to one of the following cohorts: (1) HER2+, HER2- and triple negative mBC with BM, (2) aNSCLC with BM, and (3) metastatic solid tumors with LMD. Key inclusion criteria are: age ≥18 years, ≥1 line of prior systemic treatment, histologically documented disease, ECOG 0-2, and left ventricular ejection fraction ≥50% (for all cohorts); newly diagnosed/progressing BM with ≥1 measurable brain lesion (≥10mm) by MRI (for cohorts 1 and 2); and LMD with CSF positive cytology and/or MRI (for cohort 3). Pts will receive 5.6 mg/kg of intravenous HER3-DXd on day 1 of every 21-day cycle until disease progression or unacceptable toxicity. Primary endpoints are intracranial ORR (IC-ORR) per local investigator in cohorts 1 and 2 according to RANO-BM, and 3-month OS in cohort 3. Secondary endpoints are OS, ORR, progression-free survival, time to response and duration, clinical benefit rate, safety, tolerability, quality of life evaluation and neurocognitive function evaluation by NANO scale in all cohorts. The sample size was based on Simon's two-stage design. One-sided alternative hypotheses are IC-ORR ≥25% in cohorts 1 and 2, and 3-month OS ≥25% in cohort 3. Null hypotheses are IC-ORR and 3-month OS ≤5%. Type I error is 10% and power 88%. This is the first prospective clinical trial to evaluate the intra-/extracranial efficacy and safety of HER-DXd in pretreated mBC and aNSCLC with BM, and metastatic solid tumors with LMD. If positive, TUXEDO-3 could streamline the introduction of HER3-DXd as a new treatment paradigm for these pts, who currently have very limited therapeutic options. Clinical trial information: NCT05865990. Research Sponsor: Daiichi-Sankyo; Merck Sharp & Dohme LLC.

TPS2092 Poster Session

A phase 3 randomized controlled trial of post-surgical stereotactic radiotherapy versus surgically targeted radiation therapy with GammaTile for treatment of newly diagnosed metastatic brain tumors.

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Background: Optimal management for brain metastases (BM) is crucial for outcomes of patients with metastatic cancer. The size of the BM often drives the treatment approach, with larger, symptomatic BM considered for resection followed by adjuvant stereotactic radiotherapy (SRS). SRS improves local control over resection alone. While adjuvant SRS is a well-developed standard of care for surgical BM, there are downsides that warrant consideration for alternative strategies. Local recurrence occurs in approximately 20-30% of patients, with delays to receiving adjuvant SRS associated with worse outcomes. Additionally, up to 20% of patients develop radiation necrosis. BM patients would benefit from improvements in these outcomes. GammaTile (GT Medical Technologies) is an FDA-approved device that consists of four cesium-131 radiation-emitting seeds in a collagen tile. Tiles are placed to line the cavity immediately after BM resection. This brachytherapy approach has a number of potential benefits, including an immediate start of radiation after resection when the disease burden is at a minimum; optimization of radiation dosimetry; and direct visualization of the cavity time of tile placement. Additionally, patients do not need to return as an outpatient for radiation treatment of the surgical lesion. **Methods:** This is a phase III trial with a 1:1 randomization between GammaTile brachytherapy and post-resection SRS of previously untreated BM with stratification based on patient age, duration of extracranial disease control, number of metastases, histology, maximal lesion diameter, and use of immunotherapy. The primary end point is surgical bed recurrence-free survival. Secondary end points include overall survival, physical function, neurocognitive status, quality of life, and safety. Adult patients with 1 to 4 newly diagnosed BM with a single index lesion (between 2.0 cm and 5.0 cm) planned for surgical resection are eligible. Previous and/or concurrent treatment with systemic therapies is permitted. Patients must have a Karnofsky Performance Status score of $\geq$70 and have stable systemic disease or reasonable systemic treatment options with a life expectancy of $\geq$6 months. Past radiation or surgical therapy to the index lesion or the newly diagnosed non-index lesion(s) is exclusionary, however up to 2 prior courses of SRS treatment to previously diagnosed BM are allowed if at least 15 mm from the index lesion. As of February 3 2024, 87 patients have enrolled and 80 have been randomized across 17 sites, out of a total accrual goal of 180 patients. This is a multicenter randomized controlled trial funded by GT Medical Technologies (NCT04365374). The study opened for enrollment in April 2021. The DMC last reviewed the trial in October 2023 and recommended that the trial continue as planned. Clinical trial information: NCT04365374. Research Sponsor: None.

TPS2093 **Poster Session**

A phase I/II study to assess safety and preliminary evidence of a therapeutic effect of azeliragon combined with stereotactic radiation therapy in patients with brain metastases (ADORATION).

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Background: The receptor for advanced glycation end-products (RAGE) is a multifunctional receptor which stimulates proliferation, invasion, resistance to chemotherapy and radiotherapy, and metastatic spread when activated. One of the RAGE ligands preferentially associated with brain metastasis, S100A9, has been recently identified as a specific mediator of radiotherapy resistance. RAGE also mediates neuroinflammatory pathways in the brain associated with peri-tumoral edema and cancer-related cognitive decline. Azeliragon is an oral small molecule agent that crosses the blood-brain barrier and inhibits RAGE interactions with its ligands, including S100A9. Consequently, the purpose of this study is to evaluate a new treatment paradigm with Azeliragon + stereotactic radiosurgery (SRS) for patients with brain metastasis to evaluate the safety and tolerability of the combined approach with the goal of minimizing the use of peri-procedural corticosteroids (loading dose [LD] and corticosteroid taper [CT]) as well was evaluating the potential radiosensitizing efficacy of this therapeutic combination. **Methods:** ADORATION is a single center, open-label, phase I/II cohort expansion trial to determine if azeliragon can be substituted for peri-procedural corticosteroids in patients undergoing SRS for brain metastasis. Eligible adults will have a confirmed cancer diagnosis in the last 5 years, a maximum tumor diameter of the largest brain metastasis $\leq$ 2 cm, and have discontinued corticosteroids at least 5 days prior to SRS. In phase I (n=up to 9), participants are enrolled into sequential cohorts, starting with azeliragon + SRS + LD. Depending on dose-limiting toxicities (DLTs) within 28 days of SRS, the next cohort will receive azeliragon + SRS alone or azeliragon + SRS + LD + CT. The phase II expansion cohort (n=up to 40 including the phase I cohort) will subsequently open with a primary endpoint of response rate. Azeliragon dosing includes a loading dose for 6 days followed by a continuous dose for at least 8 weeks, and SRS within 7 days of starting drug. Safety endpoints include number of DLTs and number of CNS treatment-related adverse events. Response endpoints include early brain metastasis response at 8 weeks, intracranial response at 6 and 12 months, and lesion specific local control. Neurocognitive batteries, symptom inventories, and quality-of-life questionnaires will also be administered. Three participants have been enrolled in the starting cohort and are pending DLT assessment. Clinical trial information: NCT05789589. Research Sponsor: None.

TPS2094 **Poster Session**

A phase II, multicenter, prospective study of sacituzumab govitecan in recurrent glioblastoma.

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Background: Despite decades of research, glioblastoma (GBM) remains the most common and aggressive primary brain malignancy. GBM has been shown to express trophoblast cell-surface antigen 2 (Trop2) and this expression corelates with proliferation rate, micro vessel density, histological grade and clinical survival[1,2]. Antibody drug conjugates (ADC) targeting cell surface receptors have been recently shown to produce intracranial response rates of 25-44%%[3–5]. Sacituzumab Govitecan (SG) consists of an ADC targeting Trop2 attached via linker to a chemotherapy payload, SN-38. In 2020, it received FDA approved for the treatment of metastatic triple-negative breast cancer followed by HR+/HER2- metastatic breast cancer in 2023.
Methods: This is a multi-center, open-label, prospective, single-arm phase 2 study using a 2-stage adaptive Bayesian design. Patients with GBM (IDH wild-type), recurrent following standard-of-care chemoradiation, received SG at 10mg/kg IV on days 1 and 8 of a 21 day cycle. Patients were assessed by RANO and CTCAE v5. The primary endpoint was progression-free survival of patients on SG as compared to a historical control of lomustine monotherapy. Enrollment was conducted at UT Health Science Center in San Antonio, Cleveland Clinic and Texas Oncology in Austin. A total of 23 patients have been screened with 3 screen failures and 20 patients enrolled. The study has now entered interim analysis. Trial Registration: This trial (NCT04559230) is enrolled at Clinical Trials.gov as "Sacituzumab Govitecan in Recurrent Glioblastoma": https://clinicaltrials.gov/study/NCT04559230 Funding: WK and AB have received contracted funding from Gilead. Additional support provided by an NCI Cancer Center Support Grant (P30CA016672) and an Early Clinical Investigator Award through CPRIT (RP210164). References: 1. Ning, S., et al., *TROP2 expression and its correlation with tumor proliferation and angiogenesis in human gliomas.* Neurol Sci, 2013. 34(10): p. 1745-50; 2. Harvard, B.I.o.M.a., *Broad Institute TCGA Genome Data Analysis Center (2016): Correlation between mRNA expression and clinical features;* 3.Fabi, A., et al., *T-DM1 and brain metastases: Clinical outcome in HER2-positive metastatic breast cancer.* Breast, 2018.41: p. 137-143; 4. Jacot, W., et al., *Efficacy and safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer with brain metastases.* Breast Cancer Res Treat, 2016. **157**(2): p. 307-318. Clinical trial information: NCT04559230. Research Sponsor: CPRIT; RP210164; NCI Cancer Center Support Grant; P30CA016672; Gilead.

TPS2095 **Poster Session**

Phase 1 dose-finding study to evaluate safety and tolerability of CVGBM in patients with newly diagnosed and surgically resected MGMT-unmethylated glioblastoma.

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Background: Glioblastoma (GBM) is characterized by a low mutational burden limiting the number of neoantigen targets for cancer vaccines. Vaccination against tumor-associated antigens over-presented via MHC class I and II in GBM is an alternative that has shown promise in previous trials. A previous cancer vaccine containing peptides presented by HLA-A*02:01 (class I) and some DR alleles (class II), showed evidence of peripheral and intratumoral vaccine-induced immune response against these peptides in patients with GBM. Our study will assess the safety and immunogenicity of the messenger ribonucleic acid (mRNA)-based multi-epitope vaccine CVGBM, an investigational therapeutic mRNA vaccine, encoding eight of these peptides that have demonstrated immunogenicity as peptide vaccines. CVGBM consists of a mRNA with unmodified nucleotides formulated with lipid nanoparticles. **Methods:** CV-GBLM-001 (NCT05938387) is a first-in-human, open-label, international, dose-escalation phase 1 trial. HLA-A*02:01-positive patients with newly diagnosed MGMT-unmethylated GBM (CNS WHO Grade 4), including IDH-wildtype astrocytoma with a molecular signature of unmethylated glioblastoma who have had a gross total or partial resection and who completed post-surgery radiotherapy with or without chemotherapy, are eligible to receive CVGBM. The trial comprises a dose-escalation part (Part A) followed by a dose-expansion part (Part B). In Part A, mRNA dose levels between 12 and 100 μg are being investigated and dose escalation is guided by a Bayesian logistic regression model. Patients will receive 7 doses of CVGBM by intramuscular injection on Days 1, 8, 15, 29, 43, 57, and 71, followed by 6 optional doses at 6-week intervals, up to 1 year after the first dose or until disease progression or intolerable toxicity. An independent Data and Safety Monitoring Board will recommend the dose for expansion in Part B and about 20 patients will be enrolled. Biomarkers and vaccine-induced innate and adaptive immunogenicity, including, but not limited to, systemically induced cytokines and chemokines and antigen-specific $CD4^+$ and $CD8^+$ T cells, will be monitored in the blood, and optionally in vaccine-draining lymph nodes and progressive tumors. In addition to the primary safety objectives, secondary objectives of efficacy (progression-free survival, overall survival) and patient-reported quality of life outcomes will be assessed. Trial sponsor: CureVac SE, Germany. Clinical trial information: NCT05938387. Research Sponsor: CureVac SE, Germany.

TPS2096 **Poster Session**

Azeliragon, a RAGE inhibitor, in combination with temozolomide and radiotherapy in patients with newly diagnosed glioblastoma: Phase Ib/II CAN-201 NDG trial design.

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Background: The receptor for advanced glycation end-products (RAGE) and its ligand high mobility group box 1 (HMGB1) promotes cell proliferation, invasion and angiogenesis through mitogen-activated protein kinase (MAPK), nuclear factor kappa B (NF-κB), and Akt / mTOR signaling pathways and contributes to the rise of glioblastoma (GBM) resistance to temozolomide (TMZ). Direct inhibition of RAGE showed antitumor and antiangiogenic activity in cell-based and animal preclinical models of GBM. Azeliragon, an orally available small molecule RAGE inhibitor with extensive clinical experience in patients with Alzheimer's disease, may overcome TMZ resistance and lead to enhanced efficacy of the Stupp scheme in newly diagnosed GBM. **Methods:** CAN-201 NDG is an open-label, single arm, phase Ib/II trial in Spain. Newly diagnosed GBM pts will receive azeliragon in combination with standard radiotherapy (RT) / TMZ followed by maintenance with azeliragon monotherapy. Patients should be IDH wild type, have MGMT methylation available locally, ECOG $\leq$ 2, QTC of $\leq$ 480 msec, have had a gross total or subtotal resection and be treatment naïve. Corticosteroids are allowed if administered at stable or decreasing doses. Patients with other malignancies within 5 years, presence of active infections and use of CYP 2C8 inhibitors are not allowed. The trial consists of an initial dose finding phase, in which azeliragon is administered at three dose levels in a rolling 6 dose escalation strategy: 5 mg/day (level 1), 10 mg/day (level 2) and 20 mg/day (level 3). Before the start of RT / TMZ, these dose levels have an initial loading dose for 6 days at 15 mg daily, 15 mg twice a day and 30 mg twice a day, respectively. The subsequent expansion phase may include up to 14 additional patients at the recommended phase 2 dose (RP2D). The primary objective is to determine the RP2D, defined as the dose for which $<$33% patients experience a dose limiting toxicity (DLT) within 28 days from initiation of dosing. DLTs are defined as any grade $\geq$ 3 non-hematologic adverse event (except non clinically significant investigations, fatigue, nausea or vomiting), dose delays longer than 14 days, dose reductions or limitation to administer $>$80% of expected doses. Secondary endpoints include disease control, progression-free survival according to RANO criteria, overall survival, changes in Eastern cooperative oncology group (ECOG) performance status and changes in corticosteroid requirements. The predictive and prognostic value of molecular biomarkers such as S100A9 present in blood samples will be assessed by liquid biopsy. The study received regulatory approval and accrual started in September 2023. As of January 2024, recruitment in dose level 1 was completed with 6 patients and 3 patients were already included in dose level 2. Clinical trial information: NCT05635734. Research Sponsor: CANTEX Pharmaceuticals, Inc.

TPS2097 **Poster Session**

Longitudinal stereotactic injections of oncolytic immunoactivating rQNestin34.5v.2 (CAN-3110) with concomitant biopsies for "-omic" analyses in recurrent glioblastoma (GBM).

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Background: Glioblastoma (GBM), the most common primary malignant brain tumor remains incurable. Numerous clinical trials of highly promising treatment modalities have not met efficacy objectives to support regulatory approval. One limitation in trial evaluation has been the lack of tumor sampled at various timepoints during therapy to allow analyses of the treatment's effect. Sequential biopsies have not been pursued due to possible morbidity, relative surgical inaccessibility of GBM within the brain, and quality and quantity of stereotactic biopsies to permit detailed analyses. We hypothesized that the convergence of modern neurosurgical techniques and imaging with sophisticated "omics" analyses would overcome these limitations. **Methods:** A multi-institutional phase 1 clinical trial was started in recurrent GBM (rGBM) patients treated with up to 6 stereotactic administrations of the oncolytic immunotherapy, rQNestin34.5v.2 (CAN-3110) (Ling et al. *Nature*, 2023) over 4 months (day 0, 15, 30, 60, 90 and 120) with concomitant multisector biopsies. Two cohorts of 1 x10^8 pfu per injection and 1 x 10^9 pfus per injection of rQnestin34.5v.2 are planned for a total of 6 patients per cohort using a Bayesian optimal interval (BOIN) design for dose escalation. Before each injection, multiregional sector biopsies of rGBM are undertaken and the biopsies are processed for "-omic" analyses, including single cell RNA sequencing, proteomics/phosphoproteomic/immunopeptidomics, metabolomics, spatial transcriptomics and cell profiles as well as other technologies. In addition, concomitant CSF and blood analyses are performed at the same time to longitudinally correlate biofluid markers with the treated rGBM tissues. So far, 6 patients have accrued, completing cohort 1 without experiencing DLT or SAE from the injected oncolytic rQNestin34.5v.2 and/or the multiple longitudinal procedures. A total of 316 longitudinal core biopsies were obtained from all 6 patients across the planned timepoints. The biopsies have been successfully processed for ongoing longitudinal scientific "-omic" data for the first 2 patients. Cohort 2 is scheduled to start enrollment in the spring of 2024 (NCT03152318). This abstract is submitted on behalf of the Break Through Cancer Accelerating Glioblastoma Therapies Team Lab (breakthroughcancer.org). Clinical trial information: NCT03152318. Research Sponsor: None.

TPS2098 **Poster Session**

A prospective, multicenter trial of low-intensity focused ultrasound (LIFU) for blood-brain barrier disruption for liquid biopsy in glioblastoma (LIBERATE).

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Background: Liquid biopsy in glioblastoma (GBM) is hindered by a lack of requisite circulating tumor (ct) and cell-free (cf) DNA levels in blood due to the blood-brain barrier (BBB). This limits the identification of blood-based tumor biomarkers along with the development and use of biomarker-driven systemic therapies. Real-time image-guided low intensity focused ultrasound (LIFU) combined with intravenously administered microbubble oscillators, leads to non-invasive disruption of the BBB. This trial aims to evaluate the utility of LIFU for boosting blood ctDNA and cfDNA for enhanced liquid biopsy in GBM patients. **Methods:** LIBERATE is an ongoing, prospective, multi-center, self-controlled, pivotal trial evaluating safety and technical efficacy of LIFU-based BBB disruption for increasing blood ctDNA and cfDNA levels in adults (aged 18-80 years) with GBM. Patients with suspected GBM planned for tumor biopsy or resection at ten centers in the US are being enrolled. Patients with multifocal tumors or tumors arising from deep midline, thalamus, cerebellum, or brainstem are excluded. Patients are administered IV microbubbles for enhanced sonication effects, after which MR-guided BBB disruption using a 220 kHz LIFU device is performed with real-time acoustic feedback control for effective microbubble activation. Before and after procedure, phlebotomy and MRI brain are performed to evaluate outcomes. Primary study endpoint is defined, per subject, as ratio between their cfDNA level in blood 1-hour post-LIFU procedure compared to cfDNA level in blood pre-procedure. Primary study hypothesis is that BBB disruption with LIFU leads to a $\geq$2-fold rise in blood cfDNA. The secondary hypothesis is that there exists $\geq$75% agreement between biomarker pattern in blood cfDNA sample obtained 1-hour post-LIFU and the 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 specific somatic mutations in ctDNA from blood samples collected before and after LIFU, (2) estimation of ctDNA levels post-LIFU in samples collected at 30 minutes, 1 hour, 2 hour, and 3 hour to determine the time of greatest yield, (3) correlation of MRI parameters related to grading of BBB disruption and ctDNA-based biomarkers from post-LIFU blood samples. Patient enrollment commenced in 2022 and 22 patients have been recruited by January 2024. Clinical trial information: NCT05383872. Research Sponsor: Insightec Inc.

TPS2099 **Poster Session**

A multicenter, randomized controlled phase 2b trial of survivin vaccine SurVaxM plus adjuvant temozolomide for newly diagnosed glioblastoma (SURVIVE).

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Background: Newly-diagnosed glioblastoma (nGBM) has a dismal prognosis with a median overall survival (OS) of nearly 16 months. nGBM cells have high expression of tumor-associated survivin protein. Survivin, localized to the cell surface through presentation by MHC class I molecules, is recognized by antibodies and cytotoxic T-lymphocytes (CTLs). A phase 2a trial (NCT02455557) demonstrated a median OS of 25.9 months in nGBM from a 15-amino acid-peptide-conjugate vaccine (SurVaxM), which also stimulated production of survivin-directed antibodies and anti-tumor CTL. This phase 2b randomized controlled trial (RCT) aims to further investigate the efficacy and safety of SurVaxM and adjuvant temozolomide for nGBM.
Methods: This multicenter, placebo-controlled, investigator- and patient-blinded, in-progress RCT randomizes nGBM patients receiving standard of care to either SurVaxM (arm A) or saline placebo (arm B) in a 3:2 ratio at 11 sites. Included patients have age ≥18 years, normal organ function, Karnofsky Performance Status (KPS) ≥70, receiving surgical resection with residual MRI contrast enhancement of ≤1 cm^3 within 72 hours of resection, and adjuvant temozolomide (TMZ) therapy. Patients with recurrent, multicentric, brainstem- or cerebellar-origin GBM are excluded, as well as patients on tumor-treating fields or other immunotherapies. All patients undergo 3 phases: (1) vaccine priming (VP) phase, starting within 4 weeks after completion of chemoradiation, where 4 doses of SurVaxM or Placebo are administered every 2 weeks; (2) adjuvant TMZ phase, started after ≥1 VP dose; and (3) vaccine maintenance phase, started 8 weeks after VP, with SurVaxM or placebo given every 8 weeks. TMZ phase overlaps with VP and VM phases. The primary endpoint is median OS. Assuming a 1-year survival rate of 75% in the SurVaxM arm, comparable to median OS in early phase trials, and 60% in the control arm, the required sample size consists of 137 in the SurVaxM arm and 91 in the control arm for a total sample size of 228. Accounting for dropout, the study aims to enroll 246 patients. A log-rank test stratified by KPS (70-80 and 90-100), MGMT status (methylated and unmethylated), and IDH status (mutant and wild-type) will be used for analysis. Secondary endpoints per study arm are survival at 15, 18, and 24 months, median progression-free survival, toxicity, and progression-free survival at 3, 6, and 12 months. A single sequential OS-driven interim analysis is planned when 50% of OS events (deaths) occur. 205 patients have been enrolled as of January 2024. Clinical trial information: NCT05163080. Research Sponsor: None.

TPS2100 **Poster Session**

Randomized phase IIb trial of a CMV vaccine immunotherapeutic candidate (VBI-1901) in recurrent glioblastomas.

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Background: Cytomegalovirus (CMV) antigens have been reported in over 90% of GBMs. $CD4^+$ and $CD8^+$ T cells are most frequently directed against the gB and pp65 antigens, respectively, which are immunogenic targets in a CMV-based GBM immunotherapeutic. A total of 28 first-recurrent GBM subjects were enrolled in a trial, designed as a single arm, 3-dose escalation phase (n=18) followed by a dose-expansion phase (n=10), to receive VBI-1901 (a gB/pp65 enveloped virus-like particle vaccine immunotherapeutic adjuvanted with GM-CSF) given intradermally every 4 weeks until clinical disease progression (NCT03382977). In Phase I (Part A) of the study, 3 vaccine doses (0.4μg, 2μg, and 10μg pp65) were evaluated. No DLTs or safety concerns with any of the doses. The 10μg dose was chosen for the dose-expansion phase. Injection site erythema was the most common adverse event. Vaccination with VB-1901 led to both humoral response with increase in CMV gB antibodies, and cellular response with increase in CD4+ effector memory T cells against CMV pp65 antigen; immunological responses were associated with MRI/clinical response. Among 16 subjects receiving the highest dose of VBI-1901, the disease control rate was 44%, including 2 durable partial responses, which translated into a mOS of 12.9 months. Based on these results, the study was amended into a randomized study. **Methods:** Approximately 60 adult subjects (18 years or older) with first recurrence of WHO 2016 grade IV Glioblastoma, IDH-wildtype will be randomized at a 1:1 ratio to two open-label cohorts to receive: VBI-1901 or standard of care (SOC) treatment with lomustine or carmustine. The contrast-enhancing lesion may not have an area measuring greater than 600 mm^2 (subjects with a resected first recurrence tumor, which may not be measurable after surgery, are eligible). Subjects must have a KPS ≥70, corticosteroid (dexamethasone or equivalent) dosage must be ≤ 2 mg daily that has been stable for at least 5 days before randomization into the study, and only subjects with a CD4/CD8 ratio ≥1 OR a CD4 count of ≥ 400/uL at screening are eligible, as people with a preserved immune system are more likely to respond to immunization with VBI-1901 based on the initial phase study. The primary endpoints are hierarchical. If the safety endpoint is achieved, then efficacy (overall survival) will be considered as a co-primary endpoint. Tumor response rate is a secondary endpoint with planned interim analyses. For a one-sided log rank test with an equal allocation of subjects in the two groups, 80% power and a 0.20 significance level, a total number of 47 events are needed to detect a hazard ratio for mortality of 0.6145 in the VBI-1901 cohort relative to the SOC cohort. This hazard ratio corresponds to a difference in the mOS observed previously with VBI-1901 and a historical mOS of 8 months in the SOC group. As of January 31st 2024 , 12 of 60 patients have been randomized and dosed across 8 US sites. Clinical trial information: NCT03382977. Research Sponsor: VBI Vaccines.

TPS2101 **Poster Session**

A phase 1/2 dose escalation and expansion study of sonodynamic therapy with SONALA-001 in combination with Exablate 4000 Type 2.0 MR-guided focused ultrasound in patients with progressive or recurrent glioblastoma (rGBM).

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Background: Recurrent glioblastoma (rGBM) is a lethal brain tumor with no effective therapy and an extremely poor prognosis (median survival 6 to 8 months after first recurrence). Sonodynamic therapy (SDT) is a non-invasive combination treatment that utilizes a drug, aminolevulinic acid HCL (SONALA-001), and a device, the Exablate 4000 Type 2.0, to deliver non-ablative MR-guided focused ultrasound (MRgFUS) to tumor. Preclinical studies have shown that SDT-induced sonoluminescence activates protoporphyrin IX (PpIX), which in turn generates reactive oxygen species that lead to tumor cell death and improved survival in animal glioma models. A first-in-human Phase 0 trial (NCT04559685) indicated that SONALA-001 SDT was well-tolerated and not associated with off-target cellular or radiographic effects, and provided direct evidence of reactive oxygen species formation and targeted tumor cell death in recurrent high-grade glioma (rHGG). **Methods:** SDT-202 is a Phase 1/2 multicenter, open-label, dose escalation and expansion study (NCT05370508) of 10 mg/kg iv SONALA-001 in combination with MRgFUS for SDT in patients with progressive or recurrent GBM. Treatments take place every 4 weeks. In phase 1, sonication energy escalation utilizes an accelerated titration design with a single subject for dose level 1, followed by cohorts 2 and 3 with 3+3 design for additional dose escalation. SONALA-001 is administered 6 to 12 hours prior to MRgFUS treatment. Once the RP2D is determined, Phase 2 dose expansion will enroll approximately 36 additional subjects to assess safety and efficacy of repeated cycles of SONALA-001 SDT at the optimized RP2D. Endpoints of this study are safety evaluation, maximum tolerated dose (MTD), recommended Phase 2 dose (RP2D), and determination of pharmacokinetic (PK) parameters. The Phase 2 portion will further characterize safety of RP2D along with evaluation of efficacy with PFS6 (mRANO), ORR, CBR, DOR, DOCR, TTR, and OS. Clinical trial information: NCT05370508. Research Sponsor: None.

TPS2102 **Poster Session**

Phase 1 study of multiple intracerebral doses of a neural stem cell-based oncolytic virotherapy for treatment of recurrent high-grade gliomas.

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Background: Oncolytic virotherapy is a promising cancer treatment that can directly lyse tumor cells as well as induce anti-tumor immune responses. However, clinical efficacy has been limited by rapid immune-mediated clearance of oncolytic viruses (OVs). Neural stem cell (NSC) carriers are tumor tropic and can protect OVs, allowing time for viral amplification and better distribution throughout tumors. HB1.F3.CD.21 is an immortalized, clonal human NSC line with demonstrated stability, scalability, and safety in humans (NCT01172964, NCT02015819). This NSC line was genetically modified to produce a tumor-selective, conditionally replicating adenovirus (CRAd; NSC-CRAd-S-pk7). A first-in-human clinical trial (NCT03072134) in newly diagnosed high grade glioma patients showed safety of a single intracerebral dose of NSC-CRAd-S-pk7 and determined the maximum feasible dose (MFD). Here we describe the next early phase clinical trial for development of this new NSC-based oncolytic virotherapy. **Methods:** This phase 1 study is evaluating the safety and feasibility of intracerebrally administering up to 4 weekly doses of NSC-CRAd-S-pk7 in patients with recurrent high grade gliomas. Study participants initially undergo resection of tumor followed by manual injection of the first dose of study agent into the wall of the resection cavity. Two Rickham catheters are also placed: one in the surgical cavity for subsequent administration of weekly doses of NSC-CRAd-S-pk7 and the other in the lateral ventricle to obtain serial CSF samples for correlative immunologic and safety studies. Two weeks after receiving the last dose of NSC-CRAd-S-pk7, participants undergo a second surgical procedure to remove the Rickham catheters and obtain post-treatment tissue samples. All participants are treated with the same dose of NSC-CRAd-S-pk7: 150×10^6 NSCs/1.875×10^{11} viral particles, which is the MFD that was determined in the first-in-human study. A multi-cycle toxicity equivalence range design is used to define the escalation and de-escalation rules for evaluating the four treatment schedules. Once the maximum tolerated number of weekly cycles is determined, an expansion cohort will be assessed. The study's secondary objectives include assessing the biologic activity, biodistribution, immunogenicity, safety, and preliminary clinical efficacy of NSC-CRAd-S-pk7. The estimated study sample size is 24-30 participants. Progress: The first patient began study treatment in May 2023. We are currently enrolling participants to Treatment Schedule 4. Multicenter sites for enrolling patients to the expansion cohort include City of Hope, Stanford University, Wake Forest University, and Northwestern University. Clinical trial information: NCT05139056. Research Sponsor: CIRM; Calidi Biotherapeutics Inc; Rosalinde and Arthur Gibert Fondation.

TPS2103 **Poster Session**

DIET2TREAT: A randomized, multi-center, phase 2 trial of a ketogenic diet vs standard dietary guidance in combination with standard-of-care treatment for patients with newly diagnosed glioblastoma.

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Background: Presented with a dismal prognosis and limited treatment options, many glioblastoma (GBM) patients seek complementary interventions. Of particular interest is a high-fat / low-carbohydrate diet known as the ketogenic diet (KD). Preclinical models and results from early-phase trials suggest potential benefits with KD for patients with GBM receiving standard-of-care (SOC) treatment, but definitive evidence of clinical efficacy is still lacking. **Methods:** We are conducting a multicenter randomized controlled phase 2 clinical trial of KD vs standard dietary guidance (SD) for patients with newly diagnosed GBM. All patients will receive SOC chemoradiation. Patients with newly diagnosed GBM age $\geq$ 18 years with Karnofsky Performance Status $\geq$ 70 are eligible. Exclusion criteria include inability to wean steroids below 8 mg dexamethasone/day or equivalent, Body Mass Index $<$ 21 kg/m^2, or food preferences incompatible with KD. Patients are randomized 1:1 to implement either KD (3:1 ratio between grams of fat to grams of carbohydrates + protein) or SD (based on guidelines from the American Cancer Society and American Institute of Cancer Research) for a study period of 18 weeks, starting the same time as chemoradiation. Post-randomization, all patients receive diet education, followed by in-person or virtual dietitian consultation every 2 weeks at minimum while on study. The primary objective is to assess overall survival for patients on the KD arm vs the SD arm. Secondary endpoints include assessments of progression-free survival, health-related quality-of-life (FACT-BR, FACIT-F), cognitive performance (HVLT-R, Trail-Making Test A/B), and physical activity (modified Godin leisure questionnaire, continuous activity monitoring (Fitbit)), as benefits in any of these domains would be impactful for patients. Patients randomized to the KD arm will be provided a fingerstick monitor (Keto-Mojo) to check blood ketone and glucose levels daily. Glucose and ketone levels are also periodically monitored for patients on the SD arm. Blood, tumor, and stool samples are being collected for high throughput profiling to assess the effects of KD on metabolic markers and immune response. While the primary analysis for this study is intent-to-treat, we will also perform secondary per protocol and as-treated analyses using food diaries plus glucose and ketone data. Target accrual is 170 patients over 5 years. Enrollment began in July 2023 and is ongoing. As of January 2024, the trial is open for enrollment at Cedars-Sinai Medical Center and will be opening at UCSF, Duke, Pacific Neuroscience Institute, and the Medical College of Wisconsin soon. Ten patients have been randomized so far. This trial is funded by NIH R01CA276919 and a grant from the Foundation for Metabolic Cancer Therapies and is registered as NCT05708352. Clinical trial information: NCT05708352. Research Sponsor: U.S. National Institutes of Health; R01CA276919; The Foundation for Metabolic Cancer Therapies.